BREAST CANCER
and Its
DIAGNOSIS and TREATMENT

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Breast Cancer

and Its Diagnosis and Treatment

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Dedicated To

The Memory of My Parents
Dr and Mrs. Maurice Lewison

and

The Inspiration of My Wife
Betty Fleischmann Lewison

Foreword

A number of unusual features characterize carcinoma of the breast and justify presentation in the present volume

The superficial and overt manifestations of the disease drew attention to it from earliest times Indeed, the concept and basic characteristics of malignant disease in general derive largely from observations of breast cancer The fact that the breast is an accessible and non-essential organ led to the early development of extirpative surgery in the treatment of malignant neoplasms Later, with increased understanding of the nature of the disease and its mode of spread, breast cancer was the prototype for the development and perfection of the concept of the radical operation for cancer

The occurrence of spontaneous mammary cancer in animals, and especially in mice, permitted early investigative work in the role of heredity in cancer These studies led to the work of Bittner in establishing and evaluating the milk factor as the mammary tumor agent

Another aspect of mammary cancer which makes it of peculiar interest is the early discovery of the influence of hormones on the course of the disease No other cancer has shown more encouraging results from therapeutic modifications of the hormonal environment

The wide prevalence of breast cancer in women emphasizes the importance of the problem While differences in the frequency of occurrence exist in certain races and regions, the disease is the most common malignant neoplasm in women Therefore, all physicians are challenged to familiarize themselves with the disease, to investigate it and to cope with it

The present book undertakes to assemble the known facts in regard to breast cancer Dr Lewison brings to the work the momentum of tradition set in motion by Halsted in investigation of breast cancer His collaborators are all earnest students of the disease and conspicuous contributors to the expansion of the frontiers of our knowledge of it Wide dissemination of the accumulated experience must inevitably help in the control of breast cancer, and further the progress already made in the results of treatment

GRANTLEY WALDER TAYLOR, M D

The purpose of this book has been to sift the vast store of available information concerning breast cancer combine it with practical precepts of clinical experience and make it available to all interested in the *total* care of this disease Although our accumulated knowledge of breast cancer is formidable, this knowledge is only of value if properly imparted and beneficially applied All of us must continually strive to clarify our understanding of the cause and prevention—the course and progression—of breast cancer while providing by our present practice the best possible therapy for each individual patient

Breast cancer has become an all too common universal tragedy—malign and monstrously destructive of human life Whereas progress in cancer research has given laboratory scientists the opportunity of discovering many new facts and developing deeper levels of insight into the fundamental biology of cell growth yet it remains the sole responsibility of the clinicians to utilize as promptly as possible all of the applicable information at their disposal for the care and treatment of this condition

It is of course, impossible to give even the briefest account of our entire body of knowledge concerning this disease The domain is ever increasing and even now includes such diverse disciplines as physics, chemistry genetics, bacteriology pathology, parasitology radiology medicine and surgery However, it is hoped that this book—the first comprehensive American text concerning cancer of the breast to be written in more than a quarter of a century—will serve to make new concepts of breast cancer familiar and familiar concepts new

Patience is the priceless ingredient of all progress Although the ravages of cancer have tormented mankind for many hundreds of years the promise of an early panacea is more easily said than done Today the absolute cure of cancer still remains the hope of tomorrow

In the preparation of this book I have leaned heavily upon the publications and work of other authors studying the many problems of this disease

I acknowledge my gratitude to Dr Alfred Blalock for the privilege and pleasure of being associated with the surgical staff of the Johns Hopkins Hospital and University and to Dr Grant E Ward for being afforded the opportunity of directing the program of clinical care and investigation of the Breast Clinic Division of the Tumor Clinic of the Johns Hopkins Hospital

I am deeply indebted to the able assistance of my colleagues and associates who have participated in the experimental and clinical studies of the Breast Clinic It is this wealth of clinical material which forms the basis of many of our reported observations Among these co-workers both past and present, I am grateful to Dr Robert G Chambers, Dr John G Lyons Jr, Dr L Willis Allen Dr Roy P Villasor and Dr Frances H Trimble

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It is with great pleasure that I personally acknowledge my gratitude for the section on "Anesthesia" to Dr Donald F Proctor, Anesthesiologist-in-Charge, Johns Hopkins Hospital, and to Dr Harry F Klinefelter, Jr, Instructor in Medicine, Johns Hopkins University School of Medicine, for the section on "Gynecomastia"

The drawings of surgical technique so faithfully reproduced from the operating room are the work of Mr Leon Schlossberg, Instructor, Department of Art as Applied to Medicine, Johns Hopkins University School of Medicine The clinical photographs were taken with care and fidelity by members of the Department of Photography of the Department of Art as Applied to Medicine

I am most grateful to the publishers, The Williams and Wilkins Company, of Baltimore, for their helpfulness and cooperation in the publication of this book

The merit and diligence of my secretary, Mrs Ethel L Lape, is deserving of special praise Her patience, persistence and devotion to a myriad of details incident to the publication of this book is only a partial reflection of her many capabilities

Finally, I would like to pay tribute to the labors of my distinguished colleagues and collaborators who are largely responsible for whatever success this book may enjoy

E F L

"In order to know a little well, we must be content to be ignorant of a great deal"

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CHAPTER I

The History of Breast Cancer and Its Treatment

"Let us not lightly cast aside things that belong to the past, for only with the past can we weave the fabric of the future —ANATOLE FRANCE

Introduction

Breast cancer is an ancient and elusive disease which has claimed its many victims in all walks of life at almost every age and from time immemorial Generation upon rising generation of physicians and surgeons have challenged this dread disease resorting to every therapeutic regimen considered curative at the time It seems strange indeed that despite the tremendous strides of our healing art cancer mortality has not yet reflected to any major degree the scientific solace of the wonder drugs or the bountiful benefits of an ever improving surgical skill Nevertheless living in an age of modern medical miracles we may rightly hope that this malignancy, like many sinister scourges may be ultimately conquered Until then however we must strive to increase our current treasury of knowledge and by our present practice provide the best possible treatment for each individual patient

The epic of breast surgery is a pageant of time rich in the biographies of many men of medical eminence. In the story of these skillful and courageous surgeons are prophecies of the past the revelations of which have already cast their brilliance upon the present scene and give promise of adding luster to the triumphs of the future The progress of science and surgery—microbiology and medicine—has been made possible by men whose aspirations and accomplishments have been far ahead of their time In paying respect to these praiseworthy pioneers in their crusade against breast cancer our own modest efforts are lost in admiration With deference and humility we give tribute to these venturesome spirits As Sir William Osler (39) reminds us "in the continual remembrance of a glorious past individuals and nations find their noblest inspiration "

For much of this historical material I acknowledge a great indebtedness to many sources, not the least of which are the learned and comprehensive essays of Sir D Arcy Power (44) and William A Cooper (12)

Ancient and Primitive Medicine

The oldest historical records indicate that cancer was a dire disease of both animal and man in earliest antiquity Preserved relics of prehistoric times—ancient bones and paleopathologic remnants—reveal a wide geographical and zoological distribution of malignancy Dinosaurs of the mesozoic period are said to have shown signs of cancer, and other evidences of its antiquity (19) are to be found in the treasures of the pyramids from the Etruscan tombs from Peruvian mummies and from the cuneiform tablets of

FIG 1 Breast examination From the Herbal of Pseudo-Apuleius (late 13th century), Bibloteca Medicea Laurenziana, Florence, Italy Pult 13, cod 16, fol 51 r Translation For pain in the breast of women who have milk or a tumor Grind and mix herba proserpinaca (knotgrass) with butter and apply to dispel pain wondrously and cause the tumor to disappear Translation from E Howald and H E Sigerist, editors Pseudoapulei Herbarius, Corpus Medicorum Latinorum, Vol IV, p 54 Leipzig and Berlin Teubner, 1927

the library of Nineveh However, despite its worldwide dissemination, cancer appears to have been relatively uncommon in prehistoric times Perhaps the limited survival of primitive peoples prevented them from attaining the so-called "cancer age" Sigerist (47) in the first volume of his classic masterwork of medical history refers to the curious observation that cancer of the soft tissues (including the breast) has never been found in an Egyptian mummy It must be remembered, however, that the total number of mummies which have been medically examined is probably relatively small

The earliest medical record known to modern man is the "Edwin Smith Surgical Papyrus" This relic of antiquity is regarded by historians as having been originally written in the Egyptian Pyramid Age in the Old Kingdom (3000–2500 B C) Although the manuscript gives no hint as to its author, an interesting speculation by Breasted (8) and Cooper (12) suggests that this document may very well represent in part the teachings of the oldest known physician, Imhotep, the patriarch and sage of primitive medicine who lived at a later period, the thirteenth century B C In the translation and commentary of this papyrus published by J H Breasted, the late director of the Oriental

Fig 2 Artist's conception of treatment of breast disease by cauterization with the fire drill (courtesy of Lederle Laboratories)

Institute of the University of Chicago, one finds a series of eight cases concerned with tumors or ulcers of the breast The nature of the ailment is not always clear but the available evidence indicates the disease to be breast tumors or possibly ulcers Treatment by cauterization with the fire drill (fig 2) is the oldest known reference to this practice In discussing bulging tumors of the breast the following instructions are to be found in the 'Edwin Smith Surgical Papyrus"

'If you examine a man having bulging tumors on his breast, and you find that they have spread over his breast if you place your hand upon his breast tumors and you find them to be cool there being no fever at all therein when your hand feels him they have no granulations contain no fluid give rise to no liquid discharge yet they feel protuberant to your touch you should say concerning him 'This is a case of bulging tumors I have to contend with'" The ancient Egyptian sage then goes on to say with simple honesty "There is no treatment" A brief commentary then follows, perhaps written by a more modern" contemporary something less than five thousand years ago "Bulging tumors on the breast mean the existence of swellings on the breast large spreading and hard, touching them is like touching a ball of wrappings, or they may be compared to the unripe hemat-fruit which is hard and cool to the touch like the swellings on the breast Thus, certain types of benign or malignant tumors of the breast appeared to be rather well differentiated from pyogenic mastitis and breast abscess discussed in a preceding part of the Edwin Smith papyrus

The Ebers papyrus (13) which dates from a later period (c 1600–1500 B C) is a collection of cases prescriptions and incantations without any known reference to

cancer of the breast However, a fatty tumor is described which was successfully treated "with the knife " In treating an abscess the following recommendation is made "When thou findest a purulent swelling with the apex elevated, sharply defined and of a rounded form, then sayest thou, It is a purulent tumour which is growing in the flesh—I must treat the disease with the knife " Thus, the incomplete manuscripts of ancient Egypt indicate that simple fractures and dislocations were manipulated and splinted, abscesses were opened with the cautery and later the knife, tumors were cauterized and wound surgery consisted of coaptation of the skin edges In reviewing primitive pre-Homeric Egyptian surgery there is no evidence to suggest that an operative procedure was used in the treatment of cancer of the breast

In the history of Herodotus (26), an historian who lived just prior to Hippocrates, we are told that Atossa, daughter of Cyrus and wife of Darius, had a tumor of her breast which, after a time, ulcerated and spread So long as it was small, from false modesty, she concealed it and told no one about it, but when it commenced to grow and give her trouble she sent for the famous physician Democedes (who lived in Greater Greece about 525 B C) and he cured her However, no mention of his therapeutic method is made Herodotus gives a detailed account of the prowess of Democedes, a pre-eminent physician of his times

It is a revealing commentary to note that throughout the annals of history women have never outlived their vanity Cosmetic considerations and false modesty have hindered the early diagnosis and timely treatment of breast cancer from the dawn of humanity until today Since the breast has always been an esthetic symbol of fertility and womanhood, amputation of the breast provoked mutilation of the mind as well as the body Women have taken great pride in their breasts and formerly wore decolleté dresses with disarming propriety Indeed, it was a customary and respectful form of salutation up until the seventeenth century to touch the breasts in a warm and friendly greeting Thus, through the ages, vanity has always been the death-trap of reason in the struggle toward the early diagnosis and treatment of breast cancer

Greek and Roman Medicine

The Golden Era of Greek and Roman culture is associated with the Great Hippocrates (27) who was born in the latter half of the fifth century B C on the Aegean island of Cos Known as the "father of medicine," Hippocrates (fig 3) represents all that is ex-

FIG 3 Hippocrates From a head recently discovered near Rome and now in the Ostia Museum (Courtesy of John Chadwick and W N Mann Medical Works of Hippocrates Springfield, Ill Charles C Thomas, 1951)

emplary in the western tradition of medicine Despite a prolific pen, usually ascribed to Hippocrates, and a vast collection of medical treatises, which bear the name of Hippocrates, varying in content from the technical aspects of surgery to seven complete volumes of case histories (*Epidemics*), it is indeed curious that the treatment of cancer in general and breast cancer in particular received relatively little consideration

It frequently comes as a startling revelation to find that many of our contemporary and cherished clinical observations of the present day have been so clearly described in ancient empirical works For example, the Corpus Hippocraticum," referring to occult (non-ulcerated or deep-seated) cancer makes this prophetic prognosis concerning the contra indications of surgery 'It is better to omit treatment altogether, for, if treated, the patients soon die whereas if let alone, they may last a long time'

Among the aphorisms of Hippocrates (medical truths famous enough to have added a word to the English language) one finds "Those diseases that medicines do not cure are cured by the knife Those that the knife does not cure are cured by fire Those that fire does not cure must be considered incurable' Referring specifically to cancer of the breast Hippocrates states 'A woman in Abdera had a carcinoma of the breast and bloody fluid ran from the nipple When the discharge stopped she died' A second reference to breast cancer is found in the volume relating to 'Diseases of Women'

and hard tumors appear in the breast some large and some smaller these do not suppurate but continually grow harder and harder From these grow hidden cancers When cancers are about to come on the mouth grows bitter and everything they eat tastes bitter and if you give them more to eat they refuse it and shut their mouths They become delirious their eyes are hard and they do not see clearly and pains dart from the breasts to the neck and beneath the shoulder blades thirst seizes upon them the nipples are dry and the whole body becomes emaciated the nostrils are dry and stopped up and are not elevated with respiration The breathing is superficial and they lose the sense of smell Also they do not have pain in the ears but sometimes convulsions When they have gone as far as this they do not recover but die of this disease

Aulus Cornelius Celsus (9), a Roman scholar of the early first century A D, wrote an extensive encyclopedia on agriculture, *medicine, military science*, law and philosophy of which there are only eight volumes on medicine still extant. Celsus knew a great deal more than his Hippocratic predecessors concerning the natural history of cancer He emphasized that irritation of cancer by the imprudent intervention of a physician could result in great danger to the patient Yet despite his admonitions of caution there seems to be no doubt whatsoever that early Roman surgeons of this ancient time performed heroic surgery for cancer of the breast

In regard to amputation of the breast, Celsus advised *against removal of the pectoral muscles* (an empiric procedure discarded during the Dark Ages only to be re-discovered and to find favor again almost 1800 years later) He also warned against the use of both surgery and the cautery except in early cases where the progression from what the Greeks called a "cacoethes' to a carcinoma had not yet occurred

None of these can be removed but the cacoethes the rest are irritated by every method of cure The more violent the operations are the more angry they grow Some use caustics some burning irons others remove the growth with the scalpel Nor was any person ever relieved by medicine but burning exasperates and the growth spreads rapidly until it proves fatal after excision even though a cicatrix be formed it recurs bringing with it the cause of death Whereas at the same time most people by using no violent methods to attempt the extirpation of the disease but only applying mild medicines to sooth it

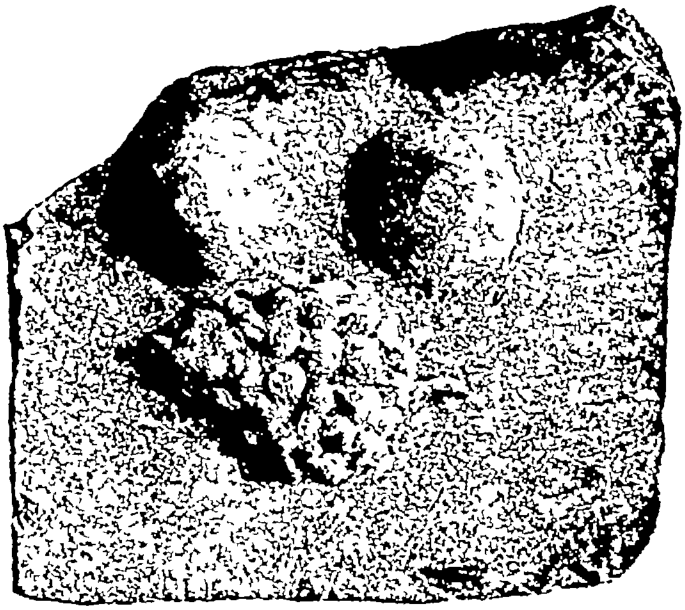

FIG 4 Limestone slab in the Cesnola Collection of the Metropolitan Museum of Art, New York The stone relief was found in the temple at Golgoi, Cyprus, and dates from the Hellenistic period (third to second century B C) This votive offering seems to represent two breasts and a nodular tumor mass It is perhaps one of the earliest representations of "cancer" in art

protract their lives, notwithstanding the disorder, to an extreme old age But no one can pretend to distinguish a "cacoethes" which is curable from a carcinoma, which is not, otherwise than by time and experiments

"Therefore, as soon as this disease is perceived, caustic medicines ought to be applied, if the disorder is alleviated, and its symptoms grow milder, we may proceed both to incision and the actual cautery, if it is immediately irritated, we may conclude that it is already a carcinoma and everything acrid and severe is to be taken away "

Galen (16) was a celebrated Greek physician who lived in the second century A D among the Romans and wrote with a remarkable prolixity Many of the vapors of Galen became the medical heritage of antiquity, some of which clouded the path of progress for untold generations The incredible authority of Galen and his sect created a dynasty of medical didactics during the Dark Ages which according to some medical historians may have been responsible for the refractoriness of medical progress until after the Renaissance To question Galen was unorthodox heresy In accord with his humoral theory of disease, Galen attributed cancer to an excess of black bile—melancholia Cancer was therefore treated by a unique dietary regimen and purgation However, if a breast tumor was readily removable, surgical excision was usually recommended

"Cancerous tumors are found in all parts of the body, but particularly in the breasts of women, after the cessation of menstruation, which, so long as it is regular, preserves good health "

Galen's description of a breast tumor and the technique for its surgical removal was incredibly discerning

"If you attempt to cure cancer by surgery, begin by cleaning out the melancholic tumor by cathartics Make accurate incisions surrounding the whole tumor so as not to leave a single root Let the blood flow and do not check it at once, but make pressure on the surrounding veins, so as to squeeze out the thick blood Then treat as in other wounds

"*We have often seen in the breast a tumor* exactly resembling the animal called the crab Just as the crab has legs on both sides of his body, so in this disease the veins extending out from the unnatural growth, take the shape of a crab's legs We have often cured this disease in its early stages, but after it has reached a large size no one has cured it without operation In all operations we attempt to excise a pathological tumor in

a circle in the region where it borders on the healthy tissue On account of the size of the vessels especially when they happen to be arteries there is immediate danger of hemorrhage, but if you use ligatures *extension of the disease* to the surrounding parts takes place If we elect to cauterize the roots of the tumor there is also no small danger connected with this when the cauterization takes place close to important organs

According to the writings of Aetius (1), Leonides of the Alexandrian School was a great physician as well as an astute clinician and careful surgeon Although his contemporaries were dominated by a nihilistic attitude toward cancer Leonides performed courageous and skillful surgery in suitable cases Careful not to operate in advanced cases, his original operative procedure for breast cancer is classic

> Placing the patient in the recumbent position I make an incision into the sound part of the breast above the cancer and immediately apply the cautery until an eschar is produced to stop the bleeding I then make another incision deep into the substance of the breast and again apply the cautery and so proceed—first cutting and then cauterizing alternately in order to restrain the bleeding So doing there can be no danger of hemorrhage When the amputation of the breast is completed again I sear the parts until they are quite dry The first cauterizings are made for the purpose of arresting the hemorrhage but the rest with the intention of eradicating the disease

Leonides of Alexandria was also the first to describe *nipple retraction* as a most important clinical sign of breast cancer

Aetius of Mesopotamia (Amida) also mentions ulcers of the breast and describes the difference between phagedenic ulcers and malignant ulcers He notes that breast cancer may be ulcerated or not but most *often the breast tumor is hard and irregular*, having extensive roots and accompanied by varicose veins Pain may be generalized and penetrating There is often sympathetic swelling and inflammation of the axillae extending often to the collar bone and scapula Poppyheads are recommended for the relief of pain

In regard to the medical treatment o breast cancer, the ancients appear to have tried many medicines—mineral, vegetable and animal—as well as innumerable psychic and physical agents, all of these, of course without success Caustics were skillfully used by the Egyptians Greeks and Romans (although there is considerable doubt that the Egyptians recognized what we now conside cancer) and this art was especially well developed by the Arabian school of medicine Since religious taboos prohibited Islamic physicians from engaging in dissection and perhaps surgery as well, the use of caustic was frequently employed with considerabl zeal "In the presence of a disease which constantly terminates in death the physician's duty consists in boldly trying every thing"

Saint Agatha, the Patron Saint of Diseases of the Breast

The descriptions of many of these primitive and brutal operations are reminiscent o the legend and tortures in the martyrdom o Saint Agatha the patron saint of diseases o the breast The story of Saint Agatha (30 starts in the third century A.D on the island of Sicily Born in either Palermo or Catania she lived in the reign of the Roman emperor Decius, during the seventh general persecution of the Christian church She came from a noble and illustrious family, and even early in life was considered destined to consecrate herself to God From her earliest infancy Saint Agatha was pre-ordained as a child of benediction

However, her great beauty, charm and social position soon captivated the heart of Quintianus, the governor of Sicily He deceitfully used the persecution of the Christians as a pretext for having her brought before his tribunal His courtship spared no means tc

FIG 5 The martyrdom of Saint Agatha by Anthony Van Dyck From the Brit J Surg 36 116, 1948

chieve its lustful designs Yet Saint Agatha purned his love and scorned the lover for his nalice toward the Church Failing thus to in her affection, Quintianus found her resumably guilty of Christian superstition nd in reprisal ordered her into the house of Aphrodesia—a wicked woman of unsavory ame and wanton reputation In this evil way e hoped to profane the Church and lead aint Agatha from the path of Christian irtue and honor However, during this eriod of imprisonment, Saint Agatha was esolute in her determination to maintain oth her faith and her chastity

After she had been kept captive for a onth in this miserable brothel, Quintianus ummoned Saint Agatha back to his court nly to find that her faith in God was unhaken Her life remained pure and undefiled, and she continued to resist the passionate ardor of Quintianus

At this point in the martyrdom of Saint Agatha there exists a diversity of legendary lore, and several harrowing versions of Saint Agatha's torture are recorded According to *the most authentic of ancient traditions*, Quintianus, in a backlash of anger, decreed that Saint Agatha "be bound to a pillar and her breasts be torn off with iron shears" She was then stripped of her garments and rolled naked upon potsherds, suffering the agony and anguish of cruel and prolonged torture Finally she was cast into a dungeon to die, but the Lord sent the prince of his apostles to heal her and restore her breasts Quintianus, upon learning of the miracle of Saint Peter, was filled with rage and furiously directed that Saint Agatha be burned

Fig 6 The martyrdom of Saint Agatha by Sebastiano del Piombo (From the University Prints Boston)

alive. But no sooner was she placed upon a blazing pyre than a violent earthquake shook the city of Catania Believing that this scourge was inflicted upon their city because of the martyrdom of Saint Agatha, the people of Catania demanded that she be immediately released Her torments at an end, she was placed in prison where she prayed to be allowed to die The Lord then took her to Himself

An equally vivid version of her exquisite sufferings places Saint Agatha upon a rack hot iron plates are applied to her flesh, and her breasts are cruelly cut off This brutal torment was accepted by the martyr with such equanimity and composure that Quintianus was infuriated During that very night a venerable old man (Saint Peter) and a young child (Christ) visited Saint Agatha in her dungeon cell and when they left, her wounds were healed and her breasts were restored

Shortly thereafter the city of Catania was shaken by a violent earthquake and two of the governor's most intimate friends were killed by falling masonry The people were in such a state of turmoil and excitement that Quintianus feared a general sedition unless Saint Agatha was liberated However she prayed to the Lord to receive her soul On February 5 she died and the Christians buried her with fitting benedictions and reverence

One year after the death of Saint Agatha the city of Catania was threatened by a fulminating volcanic eruption from nearby Mount Etna The devout and faithful Christians fled to Saint Agatha's tomb for refuge There from among her sacred relics they took her veil placed it on a lance and marched to meet the molten lava The glowing mass was nearing the city when, suddenly confronted with the sacred relic the lava swerved to one side and spared Catania Skeptics infidels and heathens who witnessed this miracle promptly paid homage to the service of Saint Agatha and were baptized and converted to Christianity

Saint Agatha is regarded as one of the patronesses of the Western church She is both a saint and a martyr whose name is enshrined in the Litany of the Saints and in the Canon of the Mass She appears in the old martyrology of Carthage and in all other martyrologies, both Greek and Latin In the sixth century Fortunatus mentions her in his poem on virginity as one of the celebrated Christian virgins and martyrs. In the Bible the Song of Solomon is said to foretell the brutal tortures of Saint Agatha She is

venerated as the patron saint of the island of Malta and of the Sicilian cities of Catania and Messina. As the patron saint of the breast, wet nurses, and bellfounders, her aid is specially sought in all of the many diseases of the breast and in fire, colic and dysentery, as well.

In art she is sometimes represented as bearing her breasts on a salver. These have been mistaken for loaves of bread and thus arose the custom of blessing bread on Saint Agatha's day. In Scandinavian countries it is believed that Quintianus had Saint Agatha brushed to death. Therefore, on February 5, Saint Agatha's day, it is traditional for girls to abstain from brushing their hair.

Dark Ages of Medicine

In the Dark Ages the medical writers were primarily concerned with the didactic dogmas and theories of treatment of their ancient predecessors. These rudimentary concepts of medicine were frequently analyzed, discussed and compared so as to dispose of any apparent contradictions. So firm was their faith in Galen that when Vesalius during the Renaissance clearly proved that Galen's concept of the hip bones was wrong, it was contended by the sixteenth century physicians that man had since changed his shape as the result of wearing tight trousers. Thus, the prospect of progress in the knowledge of medicine was hardly more than a *languishing ray of hope. Typical* of these ancient times was the statement that Apollo discovered medicine, Aesulapius extended the knowledge of medicine and that Hippocrates perfected it. The precepts of Hippocrates and the gospel of Galen were emulated by the Empiricists, and the evolution of medical science remained in abeyance.

Albucasis (3), Cordova's celebrated Spanish-Arabian surgeon, born A.D. 1013, had his doubts about the value of surgical treatment for cancer. If the cancer lies in a locality where it can be grasped in toto like the mammary gland, and especially if not fully developed, operation may be attempted, but he adds: "As for me I have never been able to cure a case nor have I known of one who has."

Lanfrank (?–1315) (28), the "father of French surgery," was still using the method of Leonides in the treatment of breast cancer despite a lapse of more than a thousand years. Henri de Mondeville (1260?–1320) (35) favored deep incision, extirpation and cauterization in small cancers, whereas arsenic and zinc chloride caustic pastes were the treatment of choice in large cancers. A rather unique method of treatment was employed by the Spanish surgeon, Francisco Arceo (1493–1571) (4), who divided the cancerous breast lengthwise and dissolved the tumor by means of a ligature. Leonard Fuchs (1501–1566) (15), a German physician and surgeon, compressed cancers of the breast by means of a lead plate. *The merit of* Guy de Chauliac (1300–1367) (10) in the treatment of cancer rests upon his authoritative surgical text, *Chirurgia Magna*. Conservative treatment including purgation and a dietary *regimen were recommended. If a* tumor seemed operable, a wide excision was performed including the removal of all the "rests."

The great army surgeon Ambroise Paré *(1510–1590) (42) was a Galenist and con*servative in the treatment of cancer. If the cancer was small, non-ulcerated and situated in a region where it could easily be removed, he excised the tumor, *taking care to go well* beyond its boundaries. Large and ulcerated lesions were treated with sweet milk, vinegar and ointments. Paré, however, recognized a relationship between breast cancer and axillary extension of the disease.

Andreas Vesalius (1514–1564) (53), a renowned Belgian anatomist in the early

Renaissance period lectured in Padua, Basel, Pisa and Bologna and spent the later years of his life as savant and body physician to the imperial court of Spain He was one of the first to oppose vigorously Galen's doctrines and discard the old anatomy The publication of the *De Humani Corporis Fabrica* in 1543 marks the beginning of modern anatomy and represents an exquisite piece of creative art Vesalius treated cancer by wide surgical excision and controlled bleeding by means of ligatures

Fabricius ab Aquapendente (1537–1619) (14) was an Italian surgeon and anatomist, famed as a professor at Padua and teacher of William Harvey He performed radical surgery for cancer only at the patient's request and decried partial excisions as worthless

An early contributor to the differential diagnosis of benign and malignant breast tumors was Marcus Aurelius Severinus (1580–1656) (46) of the school of Salerno He favored removing benign breast tumors because of the possibility of their becoming malignant He was one of the first surgeons to remove enlarged axillary nodes at the same time he radically excised breast cancer

Nicholaes Tulp (1593–1674) (51) was a Dutch anatomist and surgeon, professor of the Surgeons' Guild in Amsterdam. He commissioned Rembrandt to paint the now famous "Anatomy Lesson showing Dr Tulp during an anatomy demonstration He believed that breast cancer was contagious and described a case in which the disease was passed presumably from mistress to her servant girl.

William Clowes (1500–1634) (11) physician to Queen Elizabeth resorted to exorcism in the cure of breast cancer The simple ritual of laying on the royal hands was the queen's counterpart of curing the king s evil. The 'royal touch ' was said to have originated with Edward the Confessor, but several of his successors were somewhat *skeptical of their own divine power of faith* healing William III possessed no self delusion when he told his ailing subjects, "May God give you better health and better sense " Finally he refused to continue the practice and was consequently accused of cruelty Queen Elizabeth had a blessed ring which she wore suspended between her breasts This ring had 'the virtue of expelling infected air" and preventing disease Similar amulets of asafetida were worn until recently as a protection against occult or evil influences Charms and amulets were customarily used among all peoples as a prevention against disease Talisman, from the Arabic is a word of similar use but while talismans are regarded even today as good luck charms amulets are purely prophylactic

Although the first accurate appreciation of the nature of cancer and its differentiation from other conditions had to await the development of the microscope yet the early methods of mastectomy though barbarous and crude were surprisingly efficient and probably the result of expediency at a time when speed was of the essence Scultetus (1595–1645) (45), a famous illustrator of surgery and surgical instruments gives a very vivid portrayal of the operative procedure for cancer of the breast (fig 7) Heavy ligatures were passed through the base of the breast traction was then applied as the breast was swiftly amputated and bleeding from the operative area was quickly seared with a hot iron

Gerard Tabor (50) invented an instrument to expedite and simplify the rapidity of mastectomy This semi-circular clamp was used in amputation of the breast for cancer

The Rev John Ward (44) who was vicar of Stratford-on Avon from 1662 to 1682 and was at heart a surgeon and *pathologist*, is quoted by Sir D Arcy Power

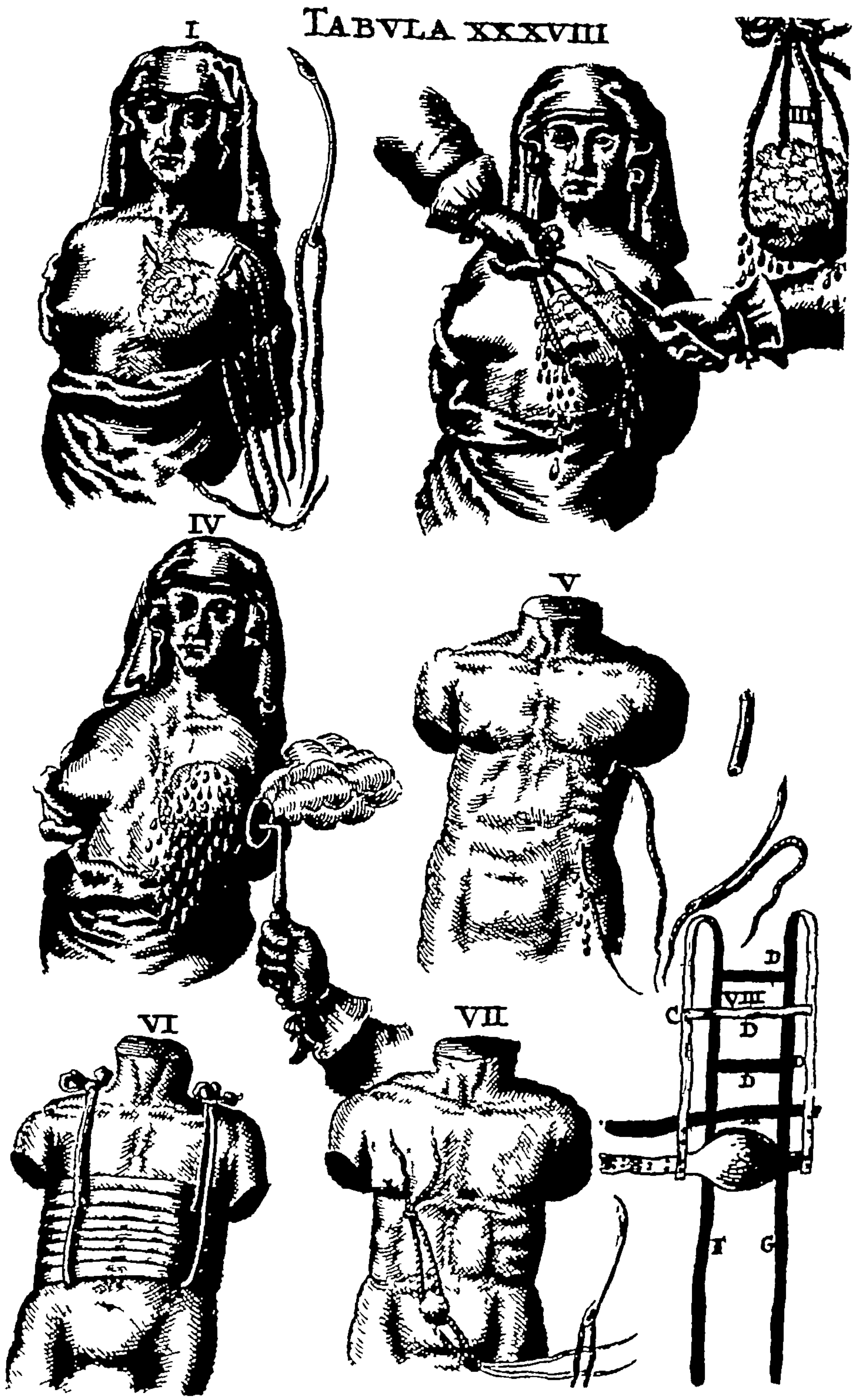

FIG 7 The operative procedure for cancer of the breast as vividly illustrated by Scultetus (1595 to 1645) The Scultetus binder—an eponymic and effective abdominal support still in surgical use—is shown in the lower left-hand corner (From Scultetus, Johannes Armamentarium Chirurgicum A Vlacq, 1655)

A cancer in Mistress Townsend's breast of Alveston taken off by two surgeons, the one's name was Clerk of Bridgnorth, the other's was Leach of Stourbridge First, they cut the skin across and laid it back, then they worked their hands in it, one above, the other below, until their hands met and so brought it out They had their needles and waxed threads ready but never

used them and also their cauterising irons but they used them not She lost not above six ounces of blood in all

Modern Medicine

One of the most enlightened surgeons of the eighteenth century was Henri Francois Le Dran (1685–1770) (29) His concept of cancer was of great importance because he completely repudiated Galen's humoral theory of the disease in favor of the idea that cancer was a local lesion in its earliest stage Le Dran believed cancer spread by way of the lymphatics to the regional nodes and he clearly described the path of metastases from breast cancer He recognized the need for early operation He dissected out enlarged axillary nodes in breast cancer, and was aware of the fact that the hope of cure was decidedly less when the axillary nodes were involved

Jean Louis Petit (1674–1750) (43), a famous French surgeon and the first director of the French Surgical Academy, set the precedent for modern mastectomy He believed that 'The roots of a cancer were the enlarged lymphatic glands, that the glands should be looked for and removed and that the pectoral fascia and even some of the fibers of the muscle itself should be dissected away rather than leave any doubtful tissue ' Petit's "Traité des Opérations was not published until twenty four years after his death however, his teachings were widely disseminated by his students and contemporaries Although the breast tumor itself was carefully avoided during the operation, as little skin as possible was removed with preservation of the nipple When breast cancer was sufficiently extensive to involve the over lying skin he recognized the need for block dissection—"where the integuments are also affected and strictly joined to the cancer there is little hope to expect a perfect cure if they are not both cleanly extirpated together ' When the cervical or supraclavicular nodes were involved, Petit considered the prognosis poor indeed The surgical skill and anatomical knowledge of Petit place him in a position of pre-eminence as an early eighteenth century master surgeon His careful removal of the axillary nodes his wide surgical excision of the primary tumor and his appreciation of dissection in continuity at a time when major surgical procedures so often resulted in widespread infection and death indicated a vision far ahead of his time and a daring for thorough and thoughtful treatment

The pessimism of the period however, is expressed by Alexander Monro (1773–1859) (37) who laments that of sixty cases of breast cancer treated surgically only four were free of the disease at the end of two years In reviewing the literature Velpeau (1856) notes that To destroy a cancerous tumor by surgical means is usually an easy matter, and but little dangerous in itself, but the question arises whether such a proceeding affords a chance of radically curing the patient This proposition is still undecided, although it has been discussed since the time of Hippocrates " According to some observers Velpeau continues ' the disease always returns after removal and operation only accelerates its progress and fatal termination This also was about the opinion of Boyer who out of one hundred operations could enumerate but four in which there was a permanent cure Scarpa who met with but three cases of success Mayo who speaks of ninety five cases *of return in one hundred* operations and MacFarlane who out of 118 operations know not of a single positive cure "However, Velpeau contends that these pessimistic views cannot be the result of rigorous observation The backward state of science at the time prevents our attaching great importance to their views "

Benjamin Bell (1749–1806) (7), surgeon to the Edinburgh Royal Infirmary, elaborated

upon the views of his predecessors in his surgical system published in 1784 In considering amputation of the breast for cancer, he taught:

"When practitioners have an opportunity of removing a cancerous breast early they should always embrace it, that as little skin as possible should be removed, and that the breast should be dissected off the pectoral muscle, which ought to be preserved If any indurated glands be observed they should be removed and particular care should be given to this part of the operation, for, unless all the diseased glands be taken away no advantage whatever will be derived from it Even when only a small portion of the breast is diseased the whole mamma should be removed The axillary glands should be dissected out by opening up the armpit, but as much skin as possible should be preserved I have done this since 1772 The older surgeons took away the skin and left the glands "

James Syme (1799–1870) (49), a Scottish surgeon writing in his "Principles of Surgery" in 1842, condemned the practice of palliative procedures in the treatment of cancer

"The only proceeding that deserves at all to be considered a remedy for cancer is removal of the morbid structure This may be done sometimes by the actual or potential cautery, but these means are very apt to destroy the disease only partially and consequently do no good, but on the contrary harm, by exciting greater activity in the portion that remains

"The knife or scissors effect the extirpation most easily and securely It would be subjecting the patient to useless pain and would bring surgery into discredit to attempt extirpation in cases where the extent or connection of the disease prevented its complete removal It is also incumbent upon the surgeon to search very carefully for glands in the course of the absorbents that may become affected since it appears that the result of operations for carcinoma when the glands are affected is almost always unsatisfactory however perfectly they may seem to have been taken away The reason of this probably is that the glands do not participate in the disease unless the system is strongly disposed to it, and consequently their removal, however freely and effectually executed, cannot prevent the pati relapse "

Syme then recommends wide excision complete resection wherever possible, " whole of it ought always to be remo however small the part of it which is ternally affected may be, and when the tis concerned is not in this way circumscrib the knife should be carried as wide possible from the tumor "

At a time when extensive surgery frequently followed by fulminating fection, when anesthesia was yet in infancy and when long-term cancer surviv following operation were a clinical curios it is indeed no wonder that amputation mastectomy was advocated only by th with a stout heart and unquenchable timism The first true appreciation of t basic nature of cancer and its differentiati from other conditions had to await t development of microscopic anatomy. Schl den, in 1838, was among the first to a preciate the significance of the cell as a u in plant structure, and Schwann in t following year recognized similar units animal tissue Muller noted the cellul structure of neoplasms Although son believed that cells could be created fro formless intercellular substances, Rem (1852) discovered cell division and Vircho and Leydig epitomized the matter by sayin "omnis cellula e cellula " The great pathol gist Virchow (1821–1902) advanced t concept that any normal cell could become cancer cell as the result of irritation Mull taught the fatalistic view that cance originated in cells which were abnormal a birth In an atmosphere of uncertainty an conflict regarding the origin and treatmen of cancer it was inevitable that this vacilla tion should be reflected in the conservati versus radical operative attack on breas cancer Prevailing pessimism indicated tha the most one could ever expect from a

operation for breast cancer was that the patient might die a little less miserably

Sir James Paget (1814–1899) (40) writing in 1853 at the dawn of surgical pathology and prior to the scientific blessings of anesthesia and asepsis (at a later date) suggests "We have to ask ourselves whether it is probable that the operation will add to the length or comfort of life enough to justify incurring the risk for its own consequences" In 235 cases of breast cancer Paget noted an operative mortality of 10 per cent There follows an eloquent dissertation on the indications and contra indications for mastectomy in a disease which seemed to him to be hopeless. Speaking of 74 cases collected by himself and M Lebert he notes "Neither of us has yet seen a case where recurrence was delayed beyond eight years" Paget adds "In deciding for or against the removal of a cancerous breast in any single case, we may, I think dismiss all hope that the operation will be a final remedy for the disease I will not say that such a thing is impossible, but it is so highly improbable that a hope of its occurring in any single case cannot be reasonably entertained"

Robert Liston (1794–1847) (33), writing at about the same period was equally disconsolate about the advantages of mastectomy

> Recourse may be had to the knife in some cases but the circumstances must be very favourable indeed to induce a surgeon to recommend or warrant him in undertaking any operation for the removal of malignant disease of the breast When the disease has been of some standing there is a considerable risk of the axillary glands having become contaminated No one could now be found so rash or so cruel as to attempt the removal of glands thus affected whether primarily or secondarily

A Velpeau (1795–1867) (52) a famous French surgeon with the opportunities for observation of a tremendous clinical practice, wrote an excellent "Treatise on the Diseases of the Breast" in 1856 The chief value of the book lies in its practical character Written at a time when the inauguration of microscopic pathology was setting the profession astir it represents the views of the "old guard" who hesitated to accord complete faith in the new cell doctrines Regarding the operative treatment of breast cancer, Velpeau favored thorough excision in preference to complete amputation "If the disease require it the pectoralis major muscle should not arrest us The smallest shade of the disease must be taken away if we are determined not to lose any chance of success However should there appear to be the necessity of interfering with the bones or resecting the ribs, we must not deceive ourselves The return of the disease is then inevitable and it would have been better not to have undertaken the operation at all"

The operative procedure of Velpeau consisted in complete excision of the tumor with its overlying skin (with preservation of the nipple when possible) and only in certain cases amputation of the breast

> If a considerable portion of the mamma is affected it is better to remove the whole gland than to preserve a few of its lobes Some surgeons have stated that as a general rule the whole mamma should be sacrificed in a case of cancer No matter how small the tumour may be I have often heard M Roux say that the return of the disease is almost certain if we remove merely a portion of the parenchymatous organ in which a cancer happens to be situated in place of amputating the whole However notwithstanding my respect for M Roux I cannot coincide in his opinion on this subject

The general or local nature of cancer excited considerable interest as well as the relationship and differentiation between benign and malignant breast tumors

New ideas which are the seeds of medical progress are said to be acquired privately

but they must be cultivated publicly Thus, Charles H Moore (38), a keen clinician and surgeon to the cancer wards of the Middlesex Hospital, presented to the professional public a most important and timely paper at a meeting of the Royal Medical and Chirurgical Society in London in 1867 Following a careful clinical investigation of the reasons for failure and recurrence following operations for breast cancer, Moore planted his seeds of learning among a fertile and enlightened audience in a paper entitled, "On the Influence of Inadequate Operations on the Theory of Cancer" Moore concluded that "Local recurrence of cancer is due to the continuous growth of fragments of the principal tumour Such recurrence may take place also in a residual part of the organ, respecting which it cannot be asserted that it was cancerous at the time of the operation Such recurrence may further happen in a structure adjoining a completely extirpated breast, and on a comparison of cases may be held to be produced by disseminated fragments of the original tumour" After a discussion of extension of the disease to the axilla Moore continues

> "It is not sufficient to remove the tumour, or any portion only of the breast in which it is situated, mammary cancer requires the careful extirpation of the entire organ The situation in which *the operation is most likely to be incomplete* is at the edge of the mamma next to the sternum When any texture adjoining the breast is involved in or even approached by the disease, that texture should be removed with the breast This observation relates *especially to skin, to* lymphatics, to much fat and to pectoral muscle *The attempt to save skin which is in any degree* unsound is of all errors perhaps the most pernicious and whenever its condition is doubtful, that texture should be freely removed
>
> "In the performance of the operation it is desirable to avoid not only cutting into the tumour, but also seeing it No actually morbid structure should be exposed lest the active microscopic elements in it should be set free and lodge in the wound Diseased axillary glands should be taken away by the same dissection as the breast itself, without dividing the intervening lymphatics, and the practice of first roughly excising the central mass of the breast, and afterwards removing *successive portions* which may be of doubtful soundness, should be abandoned Only by deliberately reflecting the flaps from the whole mamma, and detaching it first at its edge, can the *various undetected prolongations of the* tumour and outlying nodules be included in the operation"

Thus, Moore in 1867 had postulated the cardinal principles of radical mastectomy except for the consummate and essential step, the excision of the pectoral muscles

In commenting upon the past performance of inadequate mastectomy Moore states·

> "Taught without doubt by foregoing failure our surgical ancestors adopted a method that might well have been expected to prove effectual against a local recurrence of the disease They transfixed the base of the *mamma and, raising it* with ligatures, swept off the whole organ together with the skin that covered it The proceeding had a barbarous enough appearance, but it was promising and, if their knowledge of the disease had led the surgeons of the time to adopt it before the skin was hopelessly infiltrated, they must have met with more success than they *appear to have* done
>
> "It was mistaken kindness which led to a change of this mode of operating Under the influence of a clergy*man* who expressed what must have been the prevailing horror at such Amazonian surgery, the practice was changed to an incision in the integument which was *reflected in flaps and* brought together again after removal of the cancerous tumour There could have been no decrease in suffering by the prolongation of the operation and what was gained by it in neatness was *lost in life*"

In setting forth this epoch-making treatise Moore received a somewhat less than triumphant acclaim from his professional colleagues For a "man gazing on the stars is proverbially at the mercy of the puddles on the road"

Three years later, however, Joseph Lister (1827–1912) (32) extended the observations of Moore and enhanced the operation by

refining the technique of axillary exposure. Lister divided but did not remove the pectoral muscles —

Thus I have at present a patient about to leave the infirmary three weeks after the removal of the entire mamma for scirrhus all the axillary glands having been at the same time cleared out after division of both the pectoral muscles so as to permit the shoulder to be thrown back and the axilla freely exposed as is done in the dissecting room—a practice which I have for some years adopted where the lymphatic glands are affected in that disease In this case a great deal of care was certainly required for the first few days but after a week the dressings were only changed once in three days and when a fortnight had elapsed cicatrization being almost perfect a week was allowed to pass without any interference Hence on the whole the labour was considerably less than with ordinary treatment and a very much greater amount of pain would have been amply repaid by the beautiful linear cicatrix formed without the occurrence of one drop of pus and without any serious constitutional disturbance

In 1877 Mitchell Banks (5) read a paper before the Lancashire and Cheshire Branch of the British Medical Association entitled "A Plea for More Free Removal of Cancerous Growths" in which he attacked the problem that too few surgeons were practicing "extensive and sweeping removal" of breast cancer Continuing his interest in this hobby' of breast surgery Banks reported (6) the results of his operative treatment in 1882 'Surgeons, as a rule do not remove cancers of the breast They persuade their patients that they do, and they almost persuade themselves But there is always that little bit which they leave behind, and which they fondly hope will not grow because it is such a little bit Alas! that so little leaven should leaven the whole lump!"

Later in the same presentation he continues

In the present paper a principal object is to advocate the removal of the axillary glands as well as the breast in all cases whether we can feel them enlarged or not—in fact to make a clearing out of the axilla a necessary part of the operation for removal of the breast I have been quietly practising this for three or four years having been driven to the conclusions that it was the right thing to do by discovering that even in those cases where certain glands could distinctly be felt enlarged when the axilla was opened small ones were quite incapable of being felt from the outside I beg leave therefore gentlemen most strongly to urge the invariable clearing out of the axillary glands along with the removal of the breast the one operation being useless without the other As you cannot tell whether the glands are affected or not till you see them in your hand let them be always removed and so increase the patient's chances of future immunity

Concerning the use of Listerian antiseptics Banks had this to say

As a rule I employ them in hospital always But in the operation under consideration they have this one great disadvantage that the spray seriously cools down the patient and thus lowers her vitality If the operation is performed in the old fashioned and thorough and sweeping way I am now advocating there is serious shock seeing that from thirty to forty minutes is the very shortest time in which it can be satisfactorily done Now let any healthy woman get out of a warm bed strip herself naked to the waist and then go and lie down on her kitchen table for forty minutes and I shall be very much surprised if she has not a cold next day But in addition to this let a cold spray play upon her and furthermore let a great mass of heat-conserving skin and fat be carried away from the chest so that nothing but ribs and muscles intervene between the lung and the air and still let the cool spray play upon her Is not this likely to be very depressing? I am convinced that it is so and if the operator in place of doing his work rapidly niggles and fiddles about it so that the patient is kept for a long time under the combined lowering influences of cold spray anaesthetic and loss of blood then the result is that a distinct catarrhal pneumonia very speedily appears And this I have seen put the patient's life in imminent jeopardy on several occasions For this reason in private where there is but little fear of septic influences if the patient be weakly I content myself with simply washing out the wound well with carbolic solution and maintaining a modified

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antiseptic dressing In hospital I do not use the spray till the operation is pretty well completed, when I turn it on for a minute or so, and drench all the parts well before the final stitching up is done "

Dr Joseph Pancoast (1805–1882) (41), professor of general descriptive and surgical anatomy at Jefferson Medical College in Philadelphia, was one of the earliest American surgeons to emphasize the importance of *excising the breast and nodes in one piece*, but he made no mention of dividing the pectoral muscles to gain better access to the contents of the axilla Pancoast's successor at Jefferson Medical College was Samuel D Gross (17), professor of surgery, who advocated amputation of the breast but sacrificed thoroughness for conservation of skin and preservation of the axilla Samuel W Gross (18), his distinguished son, subsequently amended the surgical omissions of his father by publishing in 1880 an excellent book entitled "Tumors of the Mammary Gland " He sponsored the radical operation of Mr C H Moore in the United States and extended it to include excision of the pectoral fascia "In a remarkable paper Mr Moore, of London, in 1867 enunciated certain doctrines which, had they been widely circulated and appreciated at their full value, would possibly ere this have demolished the antiquated and utterly false teachings as to the incurability of carcinoma "

Samuel W Gross was convinced that breast cancer could be cured by thorough operations performed "before it has disseminated itself extensively locally or has tainted the general system " He believed that 'the proper procedure is to remove the entire breast and its coverings by a *circular* incision, search for any outlying lobules that may be disseminated throughout the mammary region, dissect off the fascia of the pectoral muscle, and prolong the outer portion of the incision into the axilla with a *view to its thorough exploration* " This modern doctrine and its wisdom has been amply confirmed by careful histological study

Although the skills of manual dexterity and surgical courage have been the attributes of surgeons for many, many generations, modern progress in surgery in general and cancer surgery in particular awaited the development of (1) a knowledge of anatomy and microscopic anatomy, (2) a satisfactory method of hemostasis, (3) anesthetics for safer surgery and the relief of pain, and (4) the development of antiseptic and later aseptic surgical techniques for the control of infection Prior to this period the results of the surgical treatment of breast cancer could hardly be called gratifying D Hayes Agnew (1818–1892) (2) resorted to surgery solely for its morale effect He believed that partial operation actually shortened rather than prolonged the survival time From the extensive personal experience of this excellent surgeon he could not claim a single case of permanent cure where the diagnosis was verified by microscopic examination "I do not despair of carcinoma being cured somewhere in the future, but this blessed achievement will, I believe, never be wrought by the knife of the surgeon "

The triumph of hope over pessimistic case histories—of the scientific spirit over the Dark Ages—*was sufficient to stir the souls* of a group of German surgeons who devoted a great deal of zeal and study to the development of an improved operation for the treatment of breast cancer Volkmann (54), writing in 1875, said "I make it a rule never to do a partial amputation for cancer of the breast, but *remove* the entire breast, even for the smallest tumors, and at the same time I take away a liberal piece of skin " This leading surgeon of the German school carried his incision down to the pectoral

muscle and dissected the fibers cleanly "carrying the knife parallel with the fibers of the muscle and penetrating into their interstices The pectoralis fascia is thus entirely removed I was led to adopt this procedure because on microscopic examination I repeatedly found when I had not expected it that the fascia was already carcinomatous, whereas the muscle was certainly not involved

The pectoralis major and at times the pectoralis minor muscles were excised by Volkmann in 38 patients all of whom were far advanced cases of breast cancer In 14 per cent of these patients he noted a three-year survival without evidence of recurrence. Judging from the rather meager accounts of operative breast surgery as practiced at the time Volkmann Billroth and Heidenhain were perhaps the only prominent German surgeons who had the courage and conviction to remove the pectoral muscles for breast cancer

Heidenhain (25) supported the work of Volkmann when he wrote (1889)

> I am firmly convinced from what I have seen that carcinomata when they have actually made their way into the lymphatic channels which is usually the case have always sent their advance guards to the surface of the muscle no matter what thickness of fat lies between the breast and the muscle In other words that a tumor however freely movable on the underlying parts has almost certainly advanced as far as the surface of the muscle

Heidenhain believed that cancer cells were frequently propagated through the lymphatics by muscular action. Where breast cancer had become adherent to the pectoral muscles he advocated excision of the involved muscles In a careful microscopic study of 18 cases of breast cancer he found it impossible to eradicate the disease without excision of the superficial layer of the pectoralis major

Thus although the seeds for the complete radical operation for breast cancer were already planted in the minds of many men it remained for Dr William Stewart Halsted (1852–1922) to culminate the operation and germinate the present modern method The fertile mind of Halsted was, so to speak, made up of all the minds of the preceding ages

Concealed within the text of an article on wound healing Halsted first published (20) in 1890–1891 a summary of 13 cases of breast cancer with a description of his initial surgical technique In commenting upon the operation which now bears his name Halsted says ' *About eight years ago (1882) I began not only to typically clean out the axilla in all cases of cancer of the breast but also to excise in almost every case the pectoralis major muscle, or at least a generous piece of it and to give the*

FIG 8 Portrait of Dr William Stewart Halsted by Mr Thomas Corner This picture is in the lobby of the Halsted Surgical Building of the Johns Hopkins Hospital Baltimore Md

tumor on all sides an exceedingly wide berth" Halsted then points out the difficulty in determining by gross examination alone whether or not cancer has invaded the pectoral muscle

> "From the careful microscopical examination of many very small cancers of the breast I am convinced that the pectoralis major muscle is usually at the time of the operation involved in the new growth Strange to say, no authority so far as I know suggests the advisability of always removing the pectoralis muscle or a portion of it in operations for the cure of cancer of the breast, and still stranger there are many surgeons of the first rank—surgeons in favor of methodically cleaning out the axilla—who instead of recommending the excision of the muscle advise the removal of the fascia only from the pectoral muscle Surely it is absurd not to remove the muscle when its fascia is, even to the naked eye, diseased"

In 1894 Halsted presented before the Clinical Society of Maryland (21) the results of the complete operation for the cure of cancer of the breast performed at the Johns Hopkins Hospital The basic principles of this operation "which has been attended with such surprisingly good results in our hands" was logically conceived and featured two principal premises

> "*The pectoralis major muscle, entire or all except its clavicular portion, should be excised in every case of cancer of the breast, because the operator is enabled thereby to remove in one piece all of the suspected tissues*
>
> "*The suspected tissues should be removed in one piece (1) lest the wound become infected by the division of tissues invaded by the disease, or of lymphatic vessels containing cancer cells, and (2) because shreds or pieces of cancerous tissue might readily be overlooked in a piecemeal extirpation*"

In establishing so sound a reason for removing the pectoralis major muscle it is strange indeed that Halsted neglected the underlying pectoralis minor muscle and considered it worthy of salvage Yet in 1894 Halsted's recommended operative pro merely divided the minor muscle at angles to its fibers and meticulously c away the "loose connective tissue seems to be rich in lymphatics and cc more or less fat This fat is often infil with cancer"

Four years later (1898) Halsted re "A Clinical and Histological Study o tain Adenocarcinomata of the Breast and noted. "Our present method of ting for the cure of breast cancer is ever radical than it was at the time of the w first publication on this subject The clavicular region is almost invariably c out To do this we no longer divic clavicle as we did five or six years Other changes of importance at that included the excision of both pe muscles and the immediate grafting operative wounds

The proponents of the present toward ultra-radical breast surgery very well find that precedence for the of these operations belongs to the disciples of Halsted

> "Dr Bloodgood, Instructor in Surgery, l the necks of two patients, done as many as operations each for glandular involvemen apparently saved his patients The add operations were for glands above and bel region of the neck first attacked In one of cases he entered the mediastinum from ab remove a cancerous gland, and had to ex piece of the innominate vein Dr H W Cu my house-surgeon, has in three instances c out the anterior mediastinum on one si recurrent cancer It is likely, I think, th shall in the near future remove the medi contents at some of our primary operations

For extensive disease Halsted favored ping the sheaths of the rectus, ser anterior, subscapularis, as well as latissimus dorsi and teres major "A pi the chest wall should, I believe, be exci certain cases . ."

Then as now the dangers of delayed diagnosis were well recognized by Halsted ... wish it were possible to enlighten the people as well as the physicians in all parts of this country on the subject of breast cancer, and make them realize how important it is that the operation should be done as soon as the tumor is discoverable."

In 1907 Halsted presented "The Results of Radical Operations for the Cure of Cancer of the Breast" (23) in which his initial enthusiasm for supraclavicular dissection seemed tempered by experience. The supraclavicular operation was omitted in 113 out of 232 later cases. "Before accepting the statement of anyone that he has cured a case of breast cancer with neck involvement incontrovertible proof should be demanded." Although Halsted still believed that it was "incumbent upon the surgeon to perform in many cases the supraclavicular operations," yet he remained skeptical as to the cure.

In a letter (24) to Dr William H Welch dated August 26, 1922 Halsted appraised with characteristic modesty his own contribution to the original conception of radical mastectomy

I advised and practised the removal of the entire muscle leaving in most instances the upper or subclavicular bundles (those above the cephalic vein) I divided the pectoralis minor to further facilitate the cleaning of the axilla A year or two later Willy Meyer advised removing the minor muscle as well as the major and I too came independently to the conclusion that this might better be done I insisted that all the tissues should be removed in one piece and upon the meticulous cleaning of the axilla and its aestuaries (subclavicular and supraclavicular fossae) I warned of the danger of excising pieces of malignant tumors for microscopic examination unless the operation followed immediately and was I think one of the first surgeons in this country able macroscopically to make the diagnosis of the common tumors

Contemporaneous with the publication of Halsted's second paper describing in detail his method of mastectomy in November 1894 Willy Meyer (35) presented his improved operation for breast cancer before the New York Academy of Medicine Both surgical techniques were independently conceived but were essentially similar There was no mutual indebtedness Willy Meyer advocated the routine removal of the pectoralis minor muscle an amendment acknowledged by Halsted and readily accepted in his subsequent surgical technique According to his son Herbert Willy Meyer, an accomplished breast surgeon in his own right the two operations were almost identical except for the skin incision, removal of the pectoralis minor muscle and the direction of the dissection The essence of Willy Meyer's radical operation endeavored "*to extirpate the breast the contents of the axillary and of the sub- and infra-clavicular region and the pectoral muscles in one mass*"

Whereas Willy Meyer had operated on only six patients within the three years preceding his report Halsted had had the opportunity of operating on more than 50 patients and had apparently started his studies some 12 years prior to his 1894 report of end results Thus although precedence for the radical mastectomy clearly belongs to Halsted the originality of both of these master surgeons served to focus the attention of the profession upon the basic principles of the modern radical mastectomy

Certainly one of the most fascinating features of the legend and romance of medical history is the way in which new ideas often arise simultaneously in the minds of many men Although the progress of medicine may be zigzag it is never random. Whyte (55) has recently called attention to the inexorable order that prevails in the world of science and culture and has briefly listed the best known examples of contemporaneous discovery "The telescope was claimed

by nine inventors, the thermometer by five, and nearly every major electrical invention up to the present day has involved a race for priority " In the field of medicine alone, Stern (48) has noted some 200 examples of simultaneous discovery' Vaccination was not a distinctive innovation of Jenner The immunity to smallpox which cowpox afforded was widely known at the time both in England and on the Continent Vaccination had been performed by Jesty in 1774, by Jenson and Plett in 1791 and finally by Jenner in 1796 "Curling's ulcer" was actually described by Dupuytren in 1832 some ten years before Thomas Curling's report appeared Wells (1811) and Blackall (1813) had established the correlation between dropsy and albuminous urine long before Richard Bright—one of the "great men of Guy's"—gave his celebrated account of nephritis Childbed fever was independently considered a contagious or infectious disease by Oliver Wendell Holmes in the United States, Semmelweiss in Vienna, Tarnier in Paris and Lister in London all within a relatively short time of one another

Goethe, as early as 1793, said that "the most beautiful discoveries are made not so much by men as by the period They mature in the course of time just as fruits

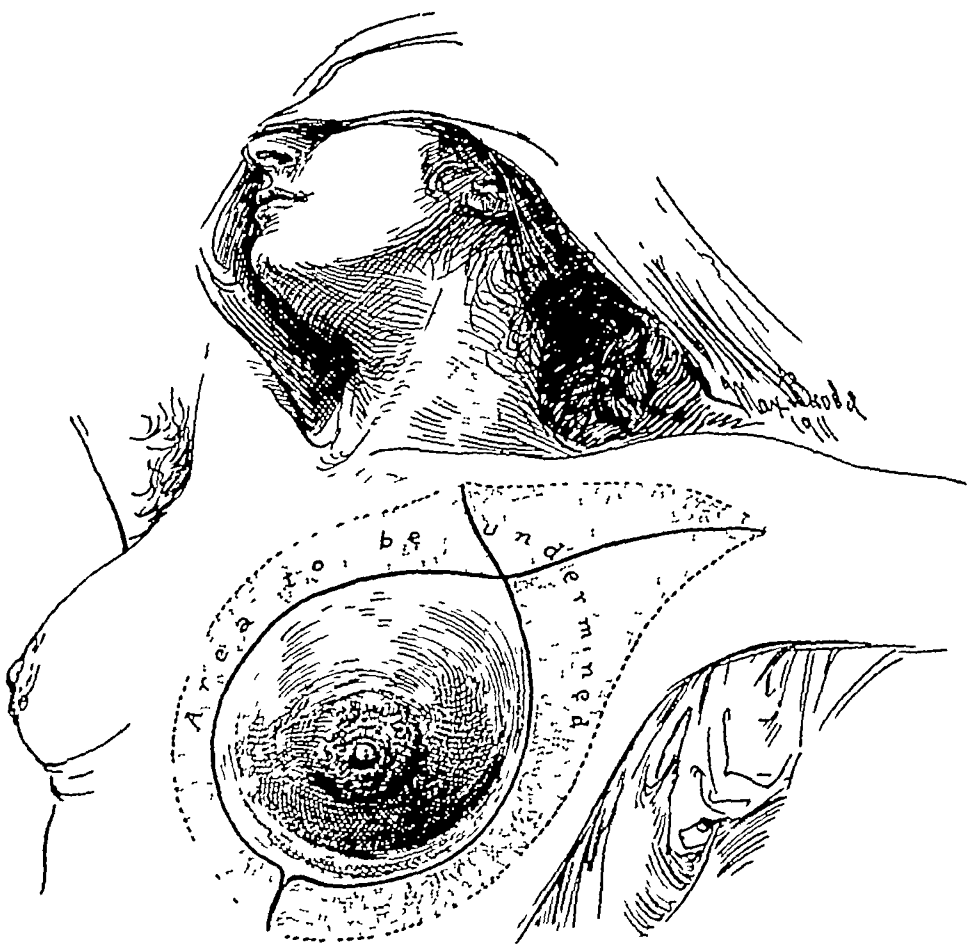

FIG 9

FIGS 9 and 10 Original and hitherto unpublished drawings of the Halsted radical mastectomy by the late Mr Max Brödel, the distinguished medical illustrator These drawings were recently discovered in, and loaned from, the early files of the Department of Art as Applied to Medicine of the Johns Hopkins University School of Medicine

fall from the tree at the same time in different gardens" Thus many innovations seem destined to be by virtue of both a man and a moment Emerson's essay on fate reminds us that, "'Tis frivolous to fix pedantically the date of particular inventions They have all been invented over and over fifty times Man is the arch machine of which all these shifts drawn from himself are toy models

'Tis hard to find the right Homer Zoroaster or Menu, harder still to find the Tubal Cain, or Vulcan or Cadmus or Copernicus or Fust or Fulton the indisputable inventor" Precedence for the modern radical mastectomy is universally bestowed upon William Stewart Halsted and rightly so Yet Halsted was certainly not the first to practice removal of the pectoralis major muscle Celsus cautioned against it almost two thousand years before, and as early as 1570 Barthélemy Cabrol, professor in Montpellier, excised the pectoralis major muscle dusted the wound with vitriol and cured the patient of breast cancer Petit in France and Volkmann and Heidenhain in Germany both favored and practiced partial removal of the pectoral muscle not infrequently However it was Halsted who by scientific surgical study logically conceived of its routine removal as an integral part of the complete operation He synthesized the best points in the techniques which had been suggested by the most advanced surgeons of the period It

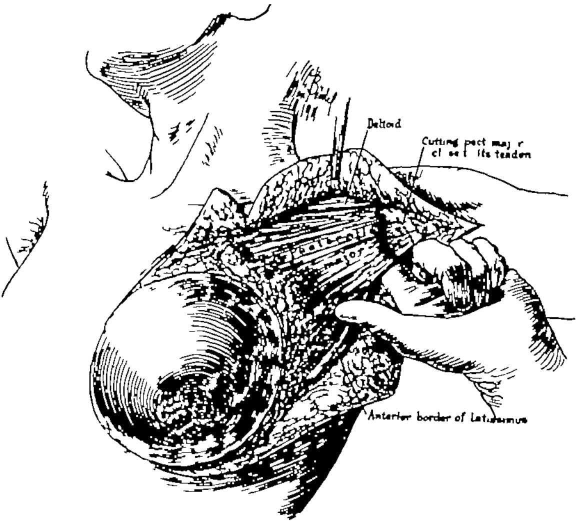

FIG 10

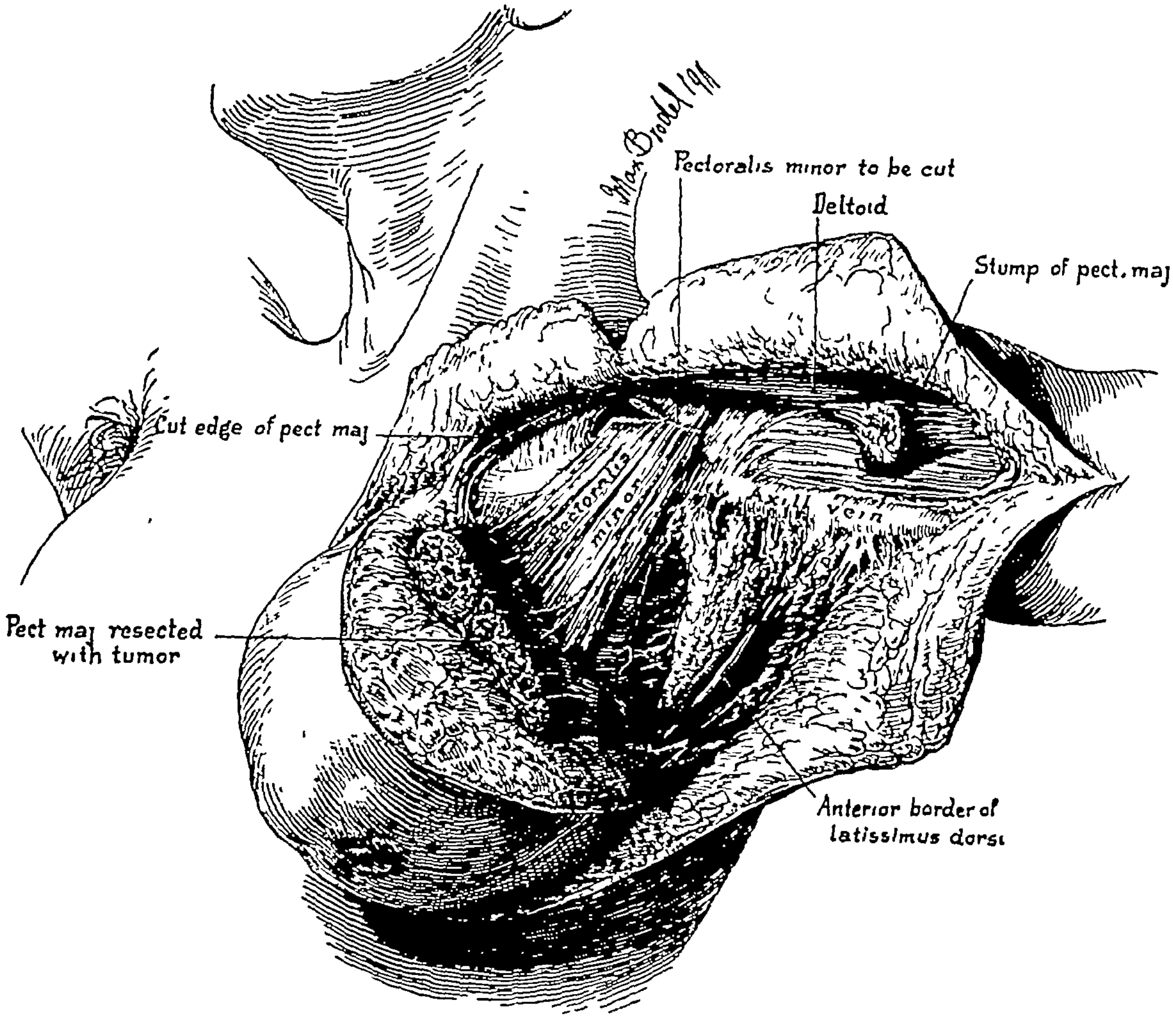

Fig 11

Figs 11 and 12 Later stages in Halsted's radical operation for breast cancer Taken from the original drawings which are now on display in the surgical library of the Halsted Building of the Johns Hopkins Hospital, used with the permission of the Johns Hopkins Press

was in the completeness of his method that he achieved a success which set a new standard in the development of breast surgery, and established a paragon of surgical precision which had no precedent in the history of the treatment of malignant disease

In a beautiful and stirring memorial address (3) the venerable Dr Matas had this to say of Dr Halsted:

"No one who has been privileged to see Dr Halsted at work on a cancer of the breast, especially during the period between 1895 and 1908, when his publications had attracted many visitors to his clinics to study his methods, could fail to recognize the reason for his extraordinary success Deeply interested in his work and absorbed in all of its details, whether operating himself or directing his staff of well trained and brilliant assistants, his delicate but far reaching dissections, by which he pursued the disease relentlessly, *without regard to esthetic effect or plastic union*; his minute and almost fastidious precautions against infection and haemorrhage, controlling the smallest bleeding point so that the total loss of blood throughout the operation was negligible, his skill and nicety in covering large skin defects with autogenic skin grafts in a way that has scarcely been equalled and has never been excelled, *and his final dressing of the wound*, covering it with silver foil and with immobilizing plaster dressings, gave the impression to the onlooker that he was seeing the performance of

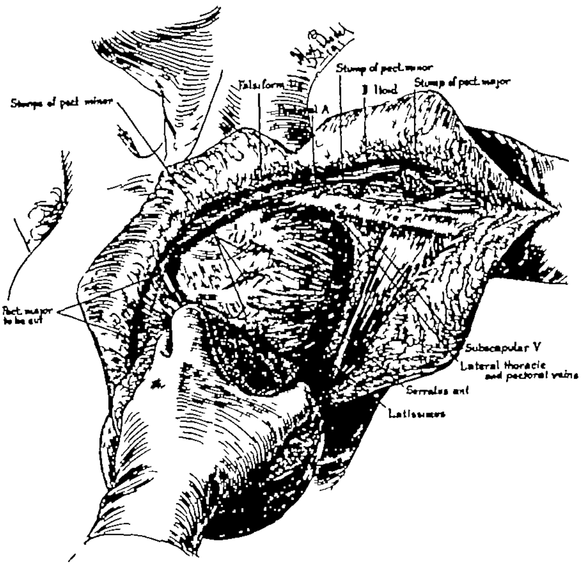

FIG 12

an artist close akin to the patient and minute labor of a Venetian or Florentine intaglio cutter or a master worker in mosaic Yet this task with all its discipline and method often consumed two and three hours was practically shockless and bloodless and was followed almost invariably by recovery

In the pageant of history the primo-movers of surgery gradually disappear and fade into an impersonal fusion. The names of such celebrated surgeons as Le Dran and Petit of France, Volkmann Billroth and Heidenhain in Germany, Moore, Lister and Banks in England and Willy Meyer and Halsted in the United States, all indicate that the contemporary pulse of the period was beating in unison throughout the world The time for radical mastectomy was ripe and its composite character and cosmopolitan development was inevitable

'Though old the thought and oft exprest,
'Tis his at last who says it best "

Lowell

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CHAPTER II

The Surgical Anatomy of the Breast[1]

RICHARD S HANDLEY, F R.C S (Eng)

It goes almost without saying that the surgeon who operates on the breast must know its anatomy There is no such thing as the *surgical* anatomy of the breast—the term falsely implies that only selected facts about its structure are necessary to operating upon it In truth, the surgeon needs to know all the anatomy of the breast, and parts of it, notably its lymphatic anatomy, better than professional anatomists To understand mammary structure it is necessary first to consider some points in its embryological development, which also help to explain some of its abnormalities

Embryology

At the sixth week of fetal life there appears in the human embryo a linear thickening of the ectoderm, slightly raised above the surface and stretching from the groin to the axilla This is the milk ridge, the caudal, two thirds of which normally disappear quite soon The middle of its cranial one third, however, shows further thickening to form the mammary primordium This reduction of the milk ridge is a species peculiarity in man which does not hold good, as a moment's thought will show, for such animals as the dog, the pig or the cow

The pectoral ectodermal thickening continues to enlarge, projecting not from the surface but down into the underlying, and now somewhat condensed, mesoderm From its deep surface a series of some twenty secondary outgrowths begins to form in the fourth month of fetal life These solid processes grow like tentacles and fan out centrifugally, becoming invested in fat In the last two months of intra-uterine life the primary downgrowth and the tentacles become canalized to form the main lobe ducts and it is from the latter that further sprouting will ultimately occur to form the small ducts and acini Even at birth only the main ducts and their larger branches are formed, and the main ducts open to the skin, not as a nipple, but in a shallow pit This pit, shortly after birth, becomes transformed by active proliferation of its subjacent mesoderm into a low nipple

Very little further growth and no essential elaboration of pattern occur until puberty, when there is some increase in branching of the main duct system Prior to puberty the nipple is inconspicuous and the areola is distinguishable from the surrounding skin only by its deeper color Microscopic sections of the areola at birth reveal slight thickening

[1] The faults and omissions of this chapter are the author's Any excellences which it may show are due to the help and constructive criticisms of members of the Middlesex Hospital and its medical school and especially to the Courtauld Professor of Anatomy Dr L W Walls, his demonstrator Dr J M Lancaster Dr A C Thackray of the Bland Sutton Institute of Pathology and Miss Hewland medical artist to the hospital

FIG 13 The mammary primordium at four months The main duct buds are beginning to form (From Dr Bradley Patten's Human Embryology by kind permission of the author and the Blakiston Company Inc)

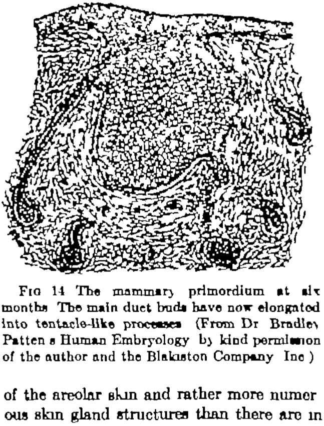

FIG 14 The mammary primordium at six months The main duct buds have now elongated into tentacle-like processes (From Dr Bradley Patten's Human Embryology by kind permission of the author and the Blakiston Company Inc)

of the areolar skin and rather more numerous skin gland structures than there are in the skin elsewhere but as fig 16 shows these gland structures bear a great similarity to the primordia of the breast, except that they do not penetrate so deeply

Gross Changes at Puberty

At puberty the breast assumes its characteristic adult shape This is achieved chiefly by the laying down of fat, and only to a slight

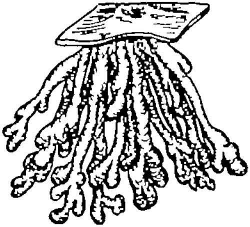

FIG 15 Reconstruction of the mammary primordium at six months (From Dr Bradley Patten's Human Embryology by kind permission of the author and the Blakiston Company Inc)

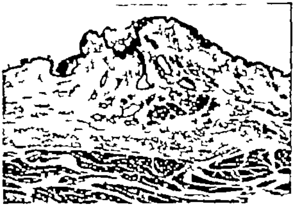

FIG 16 Section of the breast at birth. (×12) A main duct is visible opening into the nipple pit There is no glandular tissue but the branching duct system is present superficial to the pectoralis muscle fibers

extent by growth and further branching of the duct systems The nipples also grow until they project from the surface and the areola becomes thicker more vascular and with better developed areolar sebaceous glands Not until the breast experiences the stimulus of pregnancy does the full glandular structure with its numerous ducts ductules and acini manifest itself

Development Abnormalities

Inverted or crater nipples representing a persistence of the fetal condition sometimes occur through failure of the underlying

mesoderm to proliferate. Supernumerary nipples are common, particularly in men, and they usually lie along the milk line. They represent portions of the milk line which have failed to undergo the normal process of atrophy. Supernumerary breasts are rare. They occur almost exclusively in women and the axillae and groins are said to be their most usual sites. Such added adornments are occasionally reported in sites other than along the milk line and this is perhaps less surprising than it would seem at first sight when it is remembered how

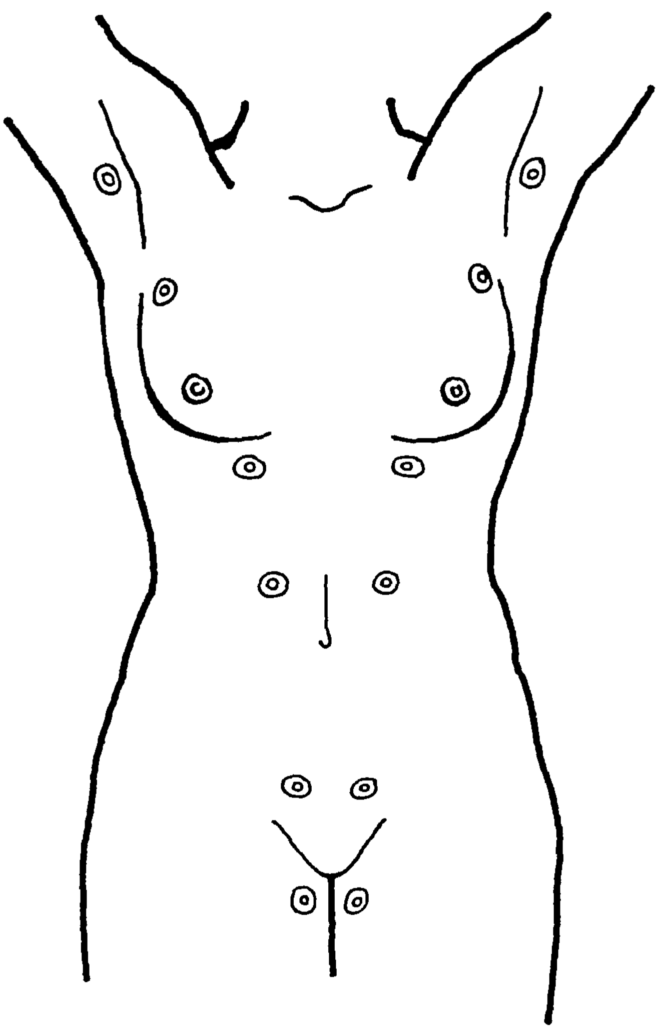

FIG. 17. Diagram to show the common sites in which supernumerary nipples and breasts occur in women. (Redrawn from Dr. Bradley Patten's Human Embryology, by kind permission of the author and the Blakiston Company, Inc.)

similar in appearance are the early developmental stages of the breast to those of sweat and sebaceous glands.

Anatomy of the Adult Female Breast

The form of the adult female breast is too well known to medical men to require description. It is rare to see the unsupported breast attain the shape which female fashion dictates and only in the early stages of pregnancy can it be said to approach its ideal in this respect. The variation in its size from one individual to another depends chiefly on the amount of fat present, and not on the bulk of the secreting tissue. Indeed the small breast often carries on its prime function of lactation better than the large breast. With advancing years the supporting tissues of the breast tend to stretch and the organ sags, a process accentuated by undue size.

The breast covers the chest wall between the second and the sixth ribs. Its medial and lateral boundaries are the edge of the sternum and the anterior axillary line. Outlying portions of breast tissue may occur beyond its gross limits and have been found as far medial as the mid line, as far lateral as the mid axillary line, as high as the clavicle and as low as the costal margin. The only constant prolongation of breast tissue is the axillary tail (of Spence) which pierces the deep fascia, through an opening known as Langer's foramen, to extend well up into the axilla. This tail makes the mammary gland proper (that is, the secreting tissue) pear-shaped, rather than circular, in its outline.

Except for the axillary tail, the breast normally lies ensheathed in the superficial fascia, though the occasional occurrence of deeper pieces of secreting tissue in the pectoral fascia has been reported. Its characteristic shape, as has been said, is due to fat, most of which lies anterior to the secreting tissue, presumably with the object of protecting the latter from injury. Gross sections

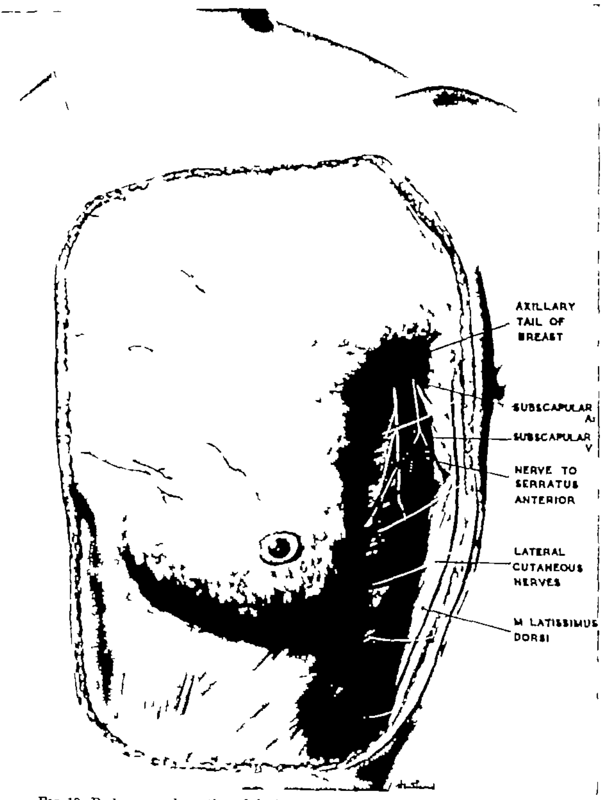

FIG 18 Preliminary dissection of the breast and lateral chest wall (from a dissection prepared by Dr J M Lancaster)

through the breast not only demonstrate this arrangement but also show thick and very irregular strands and septa of fibrous tissue which run through the secreting and fatty components of the breast from the pectoral or deep fascia to the skin The fibrous strands which pass forwards to the skin and nipple are known as the ligamenta suspensoria, or ligaments of Astley Cooper To them and to the more deeply penetrating fibrous septa the breast owes not only its support and its normal shape but also many of the physical signs which are produced by underlying disease when the latter causes scarring and shortening of the breast's fibrous supports The connective tissue of the breast may well be likened to the solid part of a marine sponge—a sponge whose interstices are filled with fat, secreting tissues and vascular pipelines

The mammary gland proper is composed of lobes, each centered round a main duct The conventional description is that there are from 12 to 20 of such lobes, but transverse sections of the nipple usually demonstrate many more than 20 main ducts, and, therefore, presumably more lobes The arrangement of the lobes round main ducts must obviously follow from the embryological sequence But these lobes are not separated from each other by distinct planes of cleavage, and the supporting connective tissue of the whole breast is so intimately continuous that it does not permit one lobe to be dissected from another Lobe identity thus depends on the main duct Despite the continuity of the supporting tissues between the lobes, injection preparations show that there is no anastomosis of the duct systems between lobes

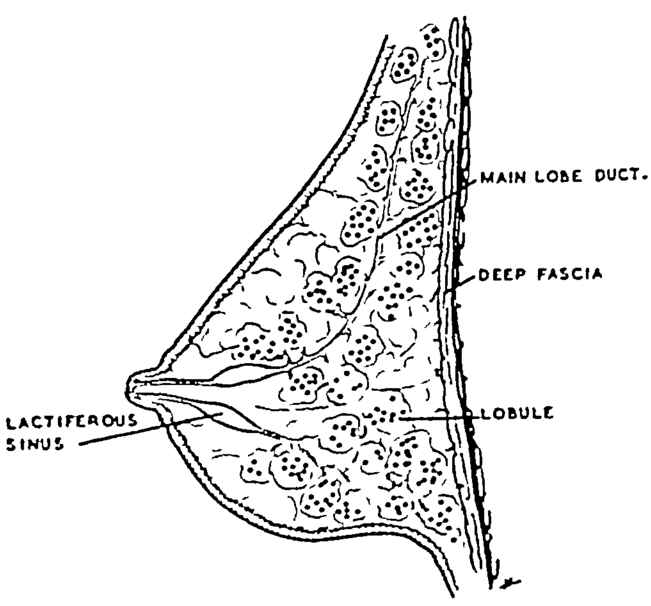

Fig. 19 Diagrammatic longitudinal section of the adult breast

The main duct in each lobe runs from the periphery of the breast to the nipple in a plane parallel with the skin Each receives many tributaries from the lobules into which the lobe is subdivided As the main duct (lactiferous duct) nears the nipple it curves forward, and swells into a fusiform dilatation, named the lactiferous sinus, the function of which is to serve as a reservoir for milk, from here it runs on to the apex of the nipple

The Nipple and Areola

The shape of the nipple, like that of the breast, is too well known to need description. The nipple is covered by thick and rather corrugated skin On its apex, and often difficult to see because of the skin corrugations, there emerge the lactiferous ducts, each opening to the surface separately from its fellows The nipple, in addition to the ducts it transmits, contains fibrous tissue which gives it its form and in which run strands of smooth muscle The function of this muscle is to erect the nipple under the mechanical stimulus of suckling Around the nipple is the areola, an area of skin about one and a quarter inches in diameter, which is bright pink in the virgin and becomes, like the nipple, more pigmented by deposits of melanin with successive pregnancies The skin of the areola, like that of the nipple, is

Fig 20 Transverse section of the adult nipple (×4) showing the thick corrugated skin and the many main ducts

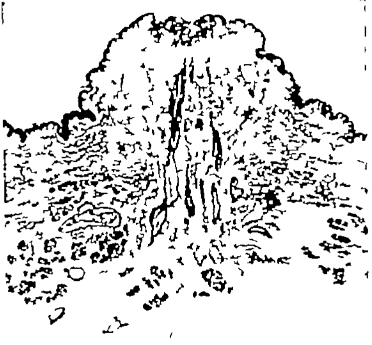

Fig 21 Section of the adult nipple (×4)

thickened and is seen in microscopic sections to show exaggerated papillary processes on its deep surface There are in the areola small subcutaneous nodules, better seen in some individuals than others These are the areolar glands (tubercles of Montgomery) They are sebaceous glands without hairs and their function is to provide protective lubrication for this area during suckling Only at the periphery of the nipple do hair and sweat gland make their appearance The nipple and areola are richly supplied with nerve endings [1]

[1] A very complete account of the nerve supply of the nipple is given by E P Cathcart F W Gairns and H S D Garven in their paper entitled 'The innervation of the human quiescent nipple with notes on pigmentation erection and hyperneury' Trans Roy Soc Edinburgh 1948 61 699

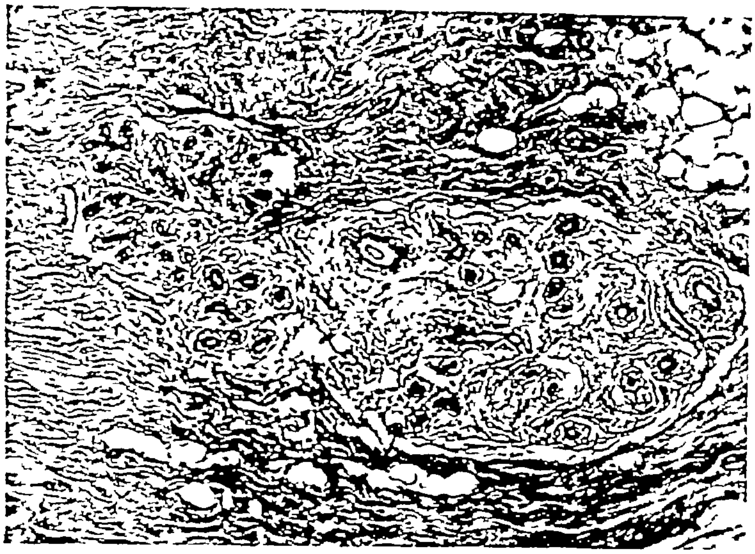

FIG 22 An adult virgin lobule (×49) The secreting elements are surrounded by the typical delicate intralobular connective tissue, contrasting with the dense less cellular interlobular connective tissue around it

John Hunter's pupil, Astley Cooper, first pointed out that the nipple lies to the lateral side of the center line of the breast and that its axis points upwards and outwards The convenience of this to the suckling child is very obvious

Anatomical Relations of the Breast

Since the breast lies within the superficial fascia, only its deep relations require mention On its deep concave surface the breast rests on muscles, separated from them by the pectoral fascia and by the branches of arteries, veins and nerves, which will be enumerated The muscle with the most extensive relation is the Pectoralis major, on which the upper and inner two thirds of the breast rests The lateral part of the mamma lies on the third, fourth and fifth digitations of the Serratus anterior Inferiorly, the breast overlaps the first digitation of the External oblique and, more medially, the upper end of the rectus sheath

Histology of the Adult Virgin Breast

The histological changes and microscopic anatomy which accompany the varying phases of breast activity, under the influence of hormones are considered in another chapter A brief note on the adult virgin breast will however serve as a summary of what may be termed its "standard" condition

Supporting Tissues

The connective tissue of the breast is of two types That of Cooper's ligaments, the fibrous septa and their prolongations around the breast lobules (the inter-lobular and inter-lobar fibrous tissues) is dense connective tissue interspersed with areas of fat and containing a few elastic fibers The connective tissue which supports the secreting elements of the lobule, that is the intralobular connective tissue, is much more delicate and more cellular and is free from fat Free cells, lymphocytes, histiocytes and fibroblasts, are present in the intra-lobular connective tissue The large ducts are supported by sheaths of dense fibrous tissue which *in the nipple is interspersed* with bundles of smooth muscle fibers These sheaths and the fibrous tissue in the nipple contain no fat

Secretory Tissues

In the lactating breast, milk is formed by blunt club-like dilatations of the terminal ductules, called alveoli There is no satisfactory evidence that alveoli exist in the virgin breast, and it is believed that in such a breast the mammary gland proper consists only of branching ducts which await the stimulus of pregnancy before budding out alveoli The smaller ducts and ductules consist of a basement membrane, inside which

is a rather irregular layer of myo-epithelial cells. Inside these is a further layer of low and somewhat irregular shaped cubical or columnar cells As the ducts get larger their epithelial lining cells become more obviously cylindrical, and then as duct size increases, the cells form into two layers The main duct of a lobe is lined by stratified epithelium which becomes squamous stratified as it nears the nipple In the non lactating breast the orifices of the ducts are plugged with a mass of keratinous debris and desquamated cells which prevents the egress of any secretion which might be formed It is to be presumed that even the resting breast must produce some scanty secretion and, since this does not escape from the nipple that it is re-absorbed

The Blood Vessels of the Breast

Arteries

The breast is generously supplied with arterial blood In pregnancy, hypertrophy of all its arteries make it an exceedingly vascular organ

The internal mammary artery brings more blood to the breast in the majority of women than all the other vessels together This artery arises from the subclavian artery, passes downwards and forwards over the dome of the pleura (where the phrenic nerve usually crosses it) and continues thence behind the medial end of the clavicle and the first costal cartilage, to reach the inner end of the first intercostal space It then descends behind the costal cartilages about a quarter of an inch lateral to the edge of the sternum to the sixth space where it divides into epigastric and musculophrenic branches Blood from it reaches the back of the breast via its anterior perforating arteries in the upper four spaces These arteries run forward, piercing the intercostal muscles and the Pectoralis major There are often two (and not as is usually stated, one) perforating arteries in each space the upper of the pair being the larger The biggest of the perforating arteries is usually the upper of the pair leaving the second space.

The vessel of second importance is the lateral thoracic artery This large artery arises from the axillary artery and descends along the outer border of the Pectoralis

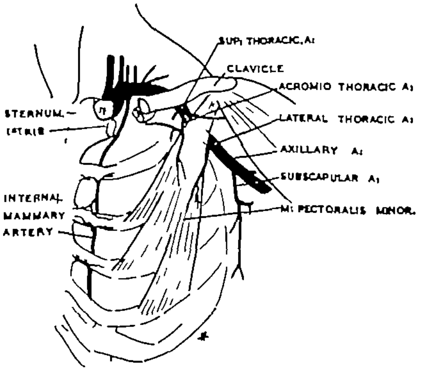

Fig 23 Diagram of the origin of arteries supplying the breast

minor muscle, sending its external mammary branches through and round the Pectoralis major to reach the breast

The only other artery of magnitude is the pectoral branch of the acromiothoracic artery, itself a branch of the axillary The acromiothoracic vessel pierces the clavipectoral fascia close to the medial edge of the Pectoralis minor muscle and almost at once gives off its pectoral branch This vessel runs down between the two pectoralis muscles, giving off branches to them, some of which reach the back of the breast

There are a number of smaller vessels The superior thoracic branch of the axillary artery, though supplying chiefly the upper chest wall, contributes to the breast The lateral perforating branches of the intercostal arteries in the upper four spaces also add their quota The subscapular artery, which is chiefly concerned with the supply of the postero-lateral muscles of the chest wall and shoulder, also sends small branches forward which contribute to the arterial supply

Fig 24 Infra-red photograph of the normal lactating breast to show subcutaneous veins

There is usually a fairly free anastomosis between the smaller branches of all these vessels, though Malmiac has shown that in some six per cent of women there is no appreciable anastomosis between the arteries approaching from the medial and lateral sides of the breast

Veins of the Breast

The veins in general follow the pattern of the arteries The subcutaneous veins over the breast are however often prominent and their engorgement or disturbance of pattern, as demonstrated by infra-red photography, has been employed as a diagnostic aid in clinical problems

The venous connections of the breast to the vertebral system of veins is of particular interest because of the theory which Batson (4) has propounded to account for the capricious distribution of some metastases in breast carcinoma Part of the venous blood from the mamma drains into the upper intercostal veins and these receive at their posterior ends tributaries from the vertebral venous plexuses Batson holds that the wide fluctuation in pressure in the vertebral vein system, associated with such efforts as coughing, could account for hemic spread of tumor emboli without the need for the latter passing through the heart His paper contains much interesting evidence on this point

Nerves of the Breast

The nerves of the breast are supplied by the anterior and lateral branches of the second to the fifth intercostal nerves With the exception of the unusually rich tactile supply to the nipple and areola, the arrangement and function of the nerves does not differ from that elsewhere in the skin The nerves subserve cutaneous sensation and carry the

sympathetic motor supply to blood vessels, hair and sweat glands in the skin There is no evidence that there is any motor nervous influence or mediation in the mechanism of breast secretion[3]

Lymphatics of the Breast

There is no part of mammary anatomy of greater importance to the surgeon than its lymphatic arrangements owing to the part the latter play in the early spread of malignant disease It is unfortunate in view of its importance that our knowledge of lymphatic anatomy is not nearly as precise as is desirable and lack of factual information leaves room for the elaboration of theories whose foundations are very uncertain Most of the work on the lymphatic pathways rests on the basis of the injection preparations, made by the old masters, on cadavers which were in an early stage of putrefaction only lately have fresh attempts been made, by means of dye injections and by tracing such substances as thorotrast by X rays to see whither the lymphatics carry material injected into the living breast prior to mastectomy

Lymphatic Vessels of the Breast

The breast being a skin structure it is probable that its lymphatic vessels have a similar basic pattern to that elsewhere in the skin Normal skin in all parts of the body is drained by four plexuses[4] a sub-papillary plexus which lies superficially in the dermis and receives the little lymph vessels from the dermal papillae an intermediate and a deep dermal plexus in the deeper part of the dermis, and a fascial plexus which lies on the deep fascia Communicating channels freely link these plexuses with one another Each, with the possible exception of the sub-papillary, is continuous in its own particular plane over the whole body but from the deep dermal and fascial plexuses arise lymphatic collecting trunks which conduct lymph to the particular lymph nodes which drain the area In the region of the breast, the mammary tissue lies between the two deeper plexuses (i.e the deep dermal and the fascial), and the communicating channels which link them run through the breast substance and drain it The exact location of the collecting trunks which drain the plexuses and the plane in which they run is uncertain but some of them at least lie in the same plane as the fascial plexus. It seems extremely probable that the subareolar plexus of Sappey, which figures in the older textbooks as the hub of the breast lymphatics, is in fact, of minor importance and concerned chiefly with the drainage of the areola and nipple[5] Sappey's plexus is not obvious in microscopic sections of the nipple area cut from breasts which have been removed for carcinoma and deposits of carcinoma cells are not seen in situations which might be consistent with their being in Sappey's plexus. In some of the older descriptions, one great collecting trunk was considered to take nearly all the lymph from the breast to the axilla. There is no evidence that this is so and it seems probable that there are many collecting trunks and that more than

[3] It seems likely that sensory impulses from the nipple may however play some part in initiating hormonal release and that nerves may thus subserve the sensory side of an arc the motor side of which is hormonal The matter is considered by W O Nelson Physiol Rev 1936 16 488

[4] The account here given is based on the paper of Gilbert Forbes in J Anat 1938 72: 399

[5] Support for the importance of Sappey's plexus has recently come from a paper by Grant Tabah and Adair (Surgery 1953 33: 71) who conclude from injection experiments with Evans blue that lymph in the breast flows in a centripetal direction towards the areola This is in direct contradiction to the results of similar work at present proceeding at the Middlesex Hospital in which Mr R Turner Warwick seems to show that lymph flows obliquely posteriorly from the parenchyma of the breast

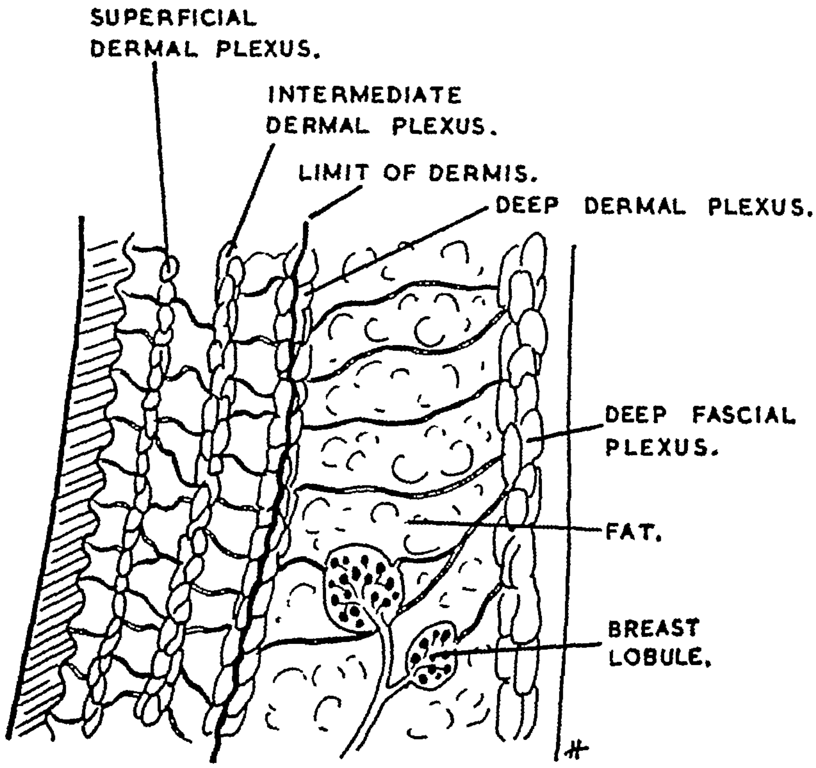

FIG. 25 Diagram to show probable relation of the breast to the lymphatic plexuses of the skin and fascia

one trunk conducts lymph to a single set of nodes. Most of the trunks wind round the lateral edge of the pectoralis muscles, but there is no doubt that some pierce these muscles

The lymphatic trunks of the breast drain principally to the axillary lymph nodes It has only lately been generally realized that a considerably smaller but nevertheless important amount of lymph passes also to the internal mammary (or parasternal) lymph nodes

The Axillary Lymph Node System

The axillary lymph node system, which is the main lymphatic exit from the breast, consists of scores of nodes, many of microscopic size, arranged round the axillary blood vessels and such of their branches as supply the breast This complex filter is one continuous whole, but it is divided into six groups to facilitate description Its arrangement is not constant, in fact, it is probable that in no two individuals is it identical When it is also remembered that the larger lymph vessels show in their walls tiny collections of a few lymphoid follicles which are believed to be capable of growing into full-sized lymph nodes if necessary, it is clear that an accurate anatomical description is not possible. Only the most approximate account can be given The immense variation also goes far towards explaining the discrepancy between the accounts of one authority and another.

With the foregoing proviso, six groups of nodes in the axillary lymph node system may be described:

1) The lateral group of nodes adjoins the lateral end of the axillary vein, distal to the point of entry of its subscapular tributary. This group drains the arm and is not involved in the pathological processes of the breast until the nodes medial to it are blocked Lymph from it drains into the central group of nodes, but there are also direct channels to the apical group

2) The subscapular group consists of six or seven nodes (with many microscopic nodes in addition) which lie on the anterior surface of the Latissimus dorsi, Teres major and Subscapularis muscles, adjoining the

subscapular blood vessels It is concerned more particularly with the drainage of the lower and outer part of the breast, and discharges to the central group

3) The pectoral group of four or five macroscopic nodes lies along the course of the lateral thoracic blood vessels and close to the lateral border of the Pectoralis minor muscle. It drains mostly the upper and outer part of the breast and its efferents run to the central group

4) The interpectoral lymph nodes (of Rotter) are not usually reckoned among the axillary system Separated from it only by the clavipectoral fascia they seem, however, entitled to be so included The group contains two or three small nodes which are much more constant than is generally believed The nodes lie around the acromiothoracic artery and its branches anterior to the clavipectoral fascia They drain the boundary area between the upper outer and upper inner quadrants, and empty into the apical group

5) The central group comprises some six fairly large nodes They are situated below the axillary vein between the lateral thoracic and subscapular blood vessels (and sometimes more medially behind the Pectoralis minor) and are embedded in the fibro-fatty tissue of the axilla They are the nodes most usually palpated clinically when they are enlarged They receive lymph from the pectoral subscapular and lateral groups al

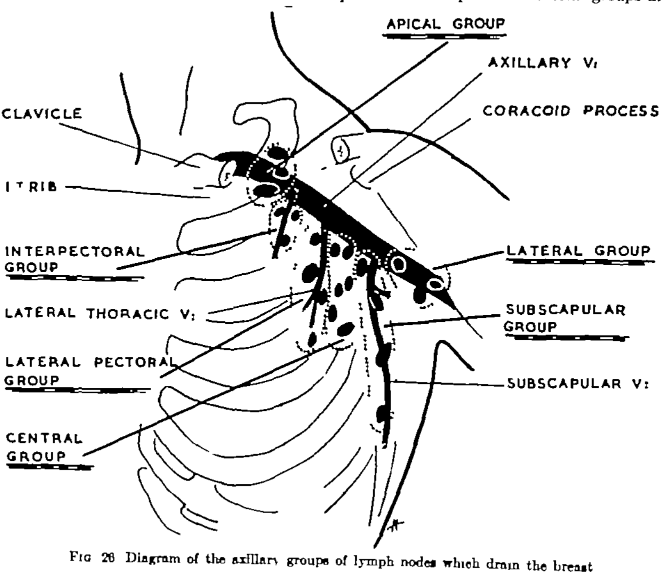

FIG 26 Diagram of the axillary groups of lymph nodes which drain the breast

ready described They are said not to receive lymph direct from the breast, but this is probably untrue, because they are sometimes found to be invaded by carcinoma when the nodes in the "feeder" groups are free from invasion They discharge centrally to the apical group of nodes.

6) The apical or sub-clavicular nodes, some eight to ten in number, lie medial to the Pectoralis minor muscle, between it and the first rib Most of the nodes are below the axillary vein, but some may be found above it and a node is also fairly often found lying high up on the neuro-vascular sheath enclosing the brachial plexus and axillary artery. A node is also commonly found at the very apex of the axilla, lying in the angle between the subclavian vein (which changes its name to the axillary vein at the outer border of the first rib) and the flat upper surface of the first rib, on which the vein rests

The apical group of nodes receives lymph from the central group and from the inter-pectoral nodes (of Rotter) It also probably receives collecting trunks which run to it direct from the upper part of the breast

The apical group discharges its lymph to the supraclavicular region The anatomical channels by which it does so are of great interest to surgeons because of the frequency with which the supraclavicular lymph nodes are invaded in carcinoma of the breast It appears that sometimes the efferents from the apical nodes gather into a single large trunk, the subclavian lymphatic trunk, which opens directly into the great veins near the junction of the internal jugular and subclavian veins, or this trunk, instead of emptying directly, may join another large lymph trunk, e g , the thoracic duct Often the subclavian lymphatic trunk runs into a sentinel node (which also receives tributaries from the supraclavicular nodes) just before opening into the veins, and supraclavicular invasion by carcinoma is then due to ret grade spread from this sentinel node So authors believe that there are direct ly phatic vascular connections between t apical and supraclavicular nodes An many doubts, it does at least seem cert that the supraclavicular nodes receive lymph direct from the breast, and that t arrangements in this region vary great between one individual and another

The Internal Mammary Lymph Chain

The first coherent description of the i ternal mammary lymphatic chain was giv by the Scottish anatomist Cruikshank 1790 The information was not incorporat in *Gray's Anatomy* (2) until 1880, and a fu investigation of the chain was not made u til Stibbe published his classical paper 1918 (10).

The internal mammary chain begins at i lower end as the efferent channel from th anterior pre-pericardial lymph nodes The latter receive lymph from the anterior pa of both sides of the diaphragm, from limited part of the anterior abdominal wa and, clinically of greatest importance, fro the upper surface of the liver The vessels c the internal mammary chain ascend th thorax, in close company with the interna mammary blood vessels, posterior to th upper six costal cartilages The lymph vessel are probably plexiform in arrangement roun the blood vessels, and they show small lymp nodes at intervals, which will shortly be dis cussed in more detail The chain drains th chest wall, including the anterior parts of th parietal pleura and the overlying muscles together with the medial part of the breast At the upper end of the thorax the lymp vessels pass posterior to the first costal carti lage and the medial end of the clavicle Their mode of termination shares, both in anatomical details and in uncertainty, that of the apical axillary group of nodes They

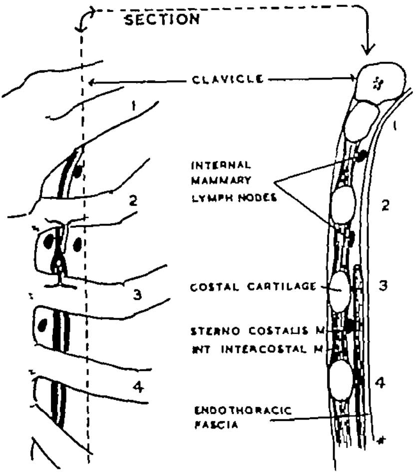

FIG 27 Diagram of the internal mammary vessels and lymph nodes seen from the front and in parasagittal section Note the usual formation of the vein in the second space by two venae comites (After a diagram in the paper by McDonald Haagensen and Stout by kind permission of the authors and the editor of Surgery)

may open into one of the adjacent great veins directly, they may join another large lymphatic trunk before opening into a vein they may terminate in the same sentinel node as receives the subclavian lymphatic trunk from the apex of the axilla in the angle between the internal jugular and subclavian veins or they may enter a separate sentinel node of their own before discharging into the veins

There is some anastomosis between the chains of either side but Rouvière (8) has only seen this at the level of the first intercostal space The anastomosis does not appear to be very free Surgeons who have examined the intercostal spaces of both sides in operable cases of breast carcinoma have found only the homolateral side invaded Pathologists however may find both sides invaded by a single mammary cancer in patients who die of the disease Other pathological processes demonstrate both known and unknown connections As might be expected general peritonitis and subphrenic suppuration cause gross enlargement and inflammatory changes in the internal mammary nodes Carbon particles or foci of tuberculosis have been observed in cases where the tracheo-bronchial lymph nodes were involved by a similar process and it seems likely that there are undescribed connections between the internal mammary chain and nodes lying deeper inside the chest

The lymph nodes associated with the internal mammary vessels are normally exceedingly small a reason no doubt for their having been for so long disregarded They commonly measure no more than one or two millimeters in diameter though they sometimes reach a size of five or six millimeters When invaded by carcinoma they nearly always remain small though nodes measur

ing two centimeters have occasionally been seen in such circumstances The nodes are usually situated either to the medial or lateral side of the internal mammary blood vessels, though they have been seen between them Nodes lie in the intercostal spaces and not behind the rib cartilages (though the latter may overlap them), a finding probably due to the pressure of the lung against the firm posterior surfaces of the cartilage, which would tend to squeeze any subpleural nodule towards the softer intercostal space

The space distribution of the nodes is uneven and inconstant. In addition to obvious macroscopic nodes, there are numerous minute ones which require the microscope for their identification and would add considerably to the number which the dissections of anatomists show Nodes are usually present in the upper three intercostal spaces, sometimes on both sides of the internal mammary blood vessels, but more often medially in the upper two spaces and laterally in the third. Nodes are not common in the fourth and fifth spaces, but the sixth space quite frequently contains one, though not so often as do the upper three spaces. It must be emphasized that the position of no single node in the whole chain can be guaranteed in any particular individual, but it is unusual for there to be no node in the first and third spaces and very unusual for there to be none in the second space Some idea of the space distribution can be gauged by adding together the figures taken from the papers of Stibbe (10), Sorensen (9) (who did not investigate the sixth space), and Ju (7) and his associates[6] (Table I)

TABLE I

No of Cases	Space	Number of Nodes (Rt + Lt Side Added Together)	Average Number of Nodes per Space (One Side Only)
	1st	394	1 0
	2nd	139	1 1
190	3rd	209	0 8
	4th	108	0 3
	5th	17	0 1
160	6th	113	0 3

A serious hiatus in knowledge of the internal mammary lymphatic system is the uncertainty as to how the nodes and trunks relate to each other, and whether the nodes are arranged in series or in parallel along the trunks It seems that the latter is more probable and that carcinomatous emboli in lymphatics can thus traverse a space without necessarily leaving an invaded node to mark their passage

Lymphatic Afferents from the Breast to the Internal Mammary Chain

The lymphatics draining the breast to the internal mammary nodes pierce the Pectoralis major muscle, in company with the anterior perforating arteries, and run through the intercostal muscles to empty into the nodes situated in the upper three spaces Lymph from the medial side of the breast is chiefly drained thus, but there is evidence to show that the central area of the breast also drains freely to the internal mammary chain.

Possible Alternative Routes of Lymphatic Drainage

It is scarcely proper to speculate in so factual a subject as anatomy Nevertheless, there remains a further possible pathway of lymphatic drainage from the breast, about which there is no definite evidence The lateral intercostal perforating arteries, particularly in the second and third intercostal

[6] The table is not completely accurate as Stibbe's paper does not allow a precise estimation of the total number of nodes found In a few instances he records that more than two nodes were found in a space For purposes of the table this has been taken to mean three nodes, though there may have been more This small inexactitude would not affect the last column

spaces, are fairly large vessels which supply a quota of arterial blood to the breast, and are accompanied by veins It is reasonable to postulate that lymphatics also accompany these vessels and that they must take some part in the drainage of the breast. If this were so such lymphatics would empty into a lymphatic plexus lying between the two layers of the internal intercostal muscle and drain into lymph nodes which lie on the necks of the ribs ie at their posterior ends Cruikshank (6) in 1790 records how he injected one of the posterior intercostal nodes and saw his injection fluid run into the body of a vertebra. We may perhaps abandon the matter at this point—it is too easy to build an elegant theoretical structure which has but a single brick as its foundation.

Lymphatic Drainage of the Breast as a Whole

We have seen that the breast drains its lymph principally to the axillary lymph nodes but that there is an important subsidiary route via the internal mammary lymphatic chain and a third possible but quite unproved lymphatic byway through the intercostal spaces. There is much overlap between the two main catchment areas but certain parts of the breast usually drain to certain lymph nodes. Fig 28 is an approximation to the state of affairs which exists, though it frequently proves fallacious It will have been noted that the axillary lymph node system is a complicated filter with relays before the lymph is discharged into the veins The internal mammary chain by comparison is small and simple and unlike the axilla is difficult to reach by surgical means It is in close apposition to vital structures throughout its length, in contra-distinction to the axillary system and its relations to the liver and the pleura are probably of considerable importance

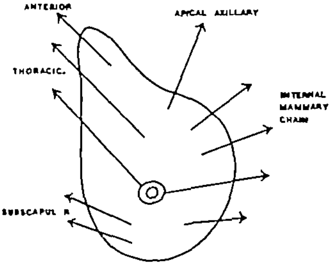

Fig 28 Diagram of the lymphatic drainage territories of the breast

Regional Anatomy bearing on the Clinical Surgery of the Breast

The surgeon who operates on the breast needs to know something of the anatomy of those regions which house its lymphatic drainage, because he may wish to ablate its lymph nodes Though space precludes a detailed consideration of regional anatomy a short summary of the normal features of the axilla and parts of the chest wall are relevant in so far as they bear on the surgery of the breast The brief description which follows is that of an operating surgeon rather than of a professional anatomist

The Axilla

The axilla may be likened to an uneven pyramid with three sides anterior posterior and medial and a base the latter being the skin of the axilla The apex of the pyramid is not a point but a hole the cervico-axillary canal which transmits the neurovascular bundle from the neck, via the axilla to the arm

The anterior wall of the axilla is of greatest importance to the surgeon because he must remove it, in whole or in part to gain free access to the axilla It consists of the two pectoral muscles The anterior of these is the

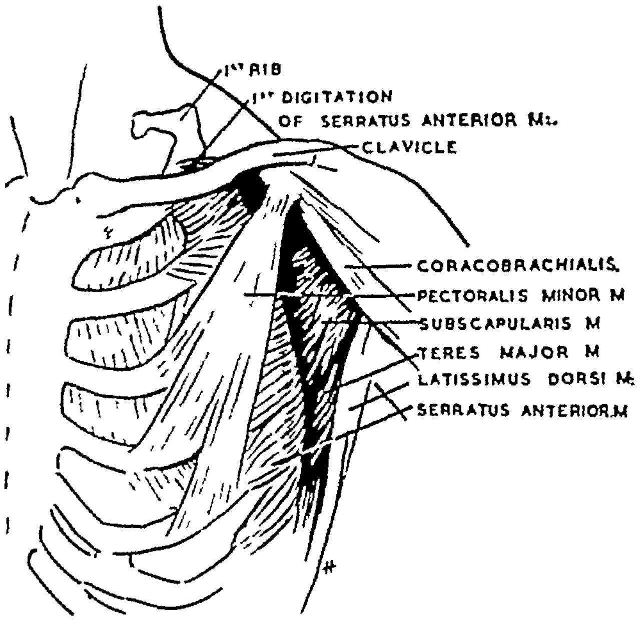

FIG 29

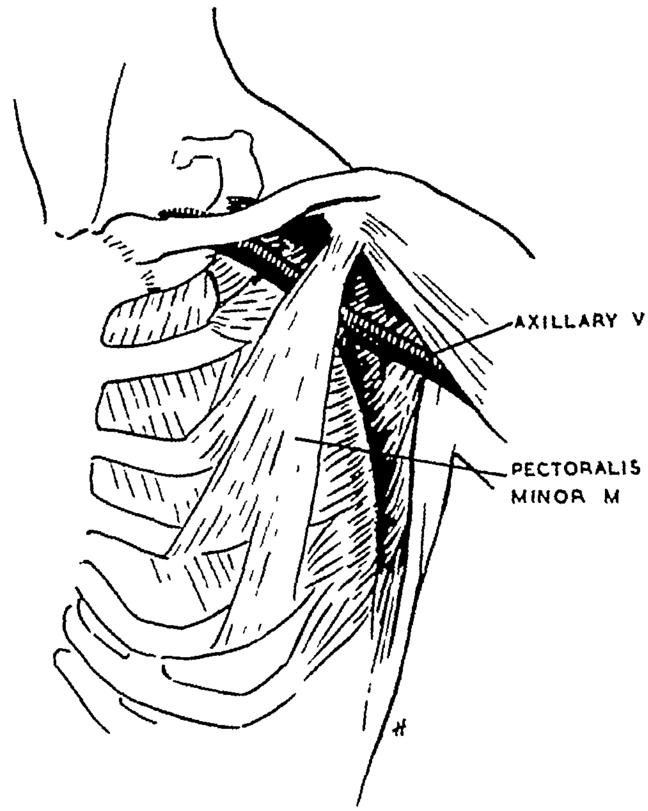

FIG 30

FIG 29 and 30 Diagram of the walls of the axilla, after removal of the Pectoralis major, which latter is not depicted The figure on the right shows the position of the axillary vein to indicate the course of the whole neurovascular bundle in relation to the axillary walls

Pectoralis major, a large thick triangular sheet of muscle originating from the anterior surface of the sternum, the cartilages of the upper six ribs and the front of the medial half of the clavicle Its mode of origin divides it naturally into sternal and clavicular heads It is inserted by tendinous fibers into the upper end of the humerus, and near its insertion gives the impression of twisting clockwise on the left side and counter-clockwise on the right as it passes laterally, so that its lower fibers run behind and above the upper fibers Behind the Pectoralis major is the Pectoralis minor It also is of elongated triangular shape, and it is considerably smaller It takes origin from the fronts of the second to the sixth ribs, and it is inserted into the coracoid process of the scapula, its fibers running at an angle of 45° to those of the Pectoralis major It is enclosed in a strong and important sheet of fascia, the clavi-pectoral fascia or costo-coracoid membrane, a structure which is always demonstrable in the operation of radical mastectomy and requires division before the contents of the axilla can properly be seen This fascia arises from the clavicle, its origin enclosing the unimportant subclavius muscle, and it fills the triangular interval between the medial border of the Pectoralis minor and the chest wall It then splits to enclose the muscle and reforms on its lateral side to run behind the Pectoralis major and to become attached to the axillary fascia which is immediately subjacent to the skin of the axilla The Pectoralis minor and the clavi-pectoral fascia are the real surgical key to the axilla The Pectoralis major can be retracted sufficiently when the arm is adducted to give fair exposure of the whole axilla, but unless the Pectoralis minor is sectioned or removed, nothing like an adequate view of the axillary structures can be obtained.

The medial wall of the axilla is formed by

the ribs and intercostal muscles of the upper chest wall, covered by the upper four or five slips of the Serratus anterior muscle This large muscle which extends further down the chest wall than the axilla, arises from the antero-lateral surfaces of the upper eight ribs by digitations which converge to pass posteriorly and enwrap the lateral chest wall The Serratus anterior is inserted into the vertebral border of the scapula

The posterior wall of the axilla is mainly formed by the Subscapularis and Latissimus dorsi muscles, the Teres major taking only a small and unimportant part The Subscapularis muscle takes origin from the anterior surface of the scapula which it almost completely covers and converges to its insertion into the humerus. The Latissimus dorsi is a very extensive muscle arising from the spines of the vertebrae below the sixth thoracic and the crest of the ilium Its complex and distant origin is of no moment in the present context. It converges to its insertion on the upper end of the humerus and is of importance to the surgeon not only as a part of the posterior wall of the axilla but also because its anterior edge forms the posterior axillary fold, an important landmark, it indicates the posterior limit to which dissection is carried in the operation of radical mastectomy

The apex of the axillary pyramid is the cervico-axillary canal, bounded by the outer border of the first rib on the medial side, the upper border of the scapula postero-laterally and the back of the clavicle antero-laterally The base of the pyramid is formed by the tough axillary fascia underlying the skin of the axilla The latter is generously provided with sweat and apocrine glands

The contents of the axilla are the axillary neurovascular bundle with certain of its branches the conjoined tendon of the coracobrachialis and biceps muscles (sometimes called the lateral wall of the axilla but so narrow as hardly to deserve the dignity of that term) certain vessels and nerves entering from the intercostal spaces the axillary

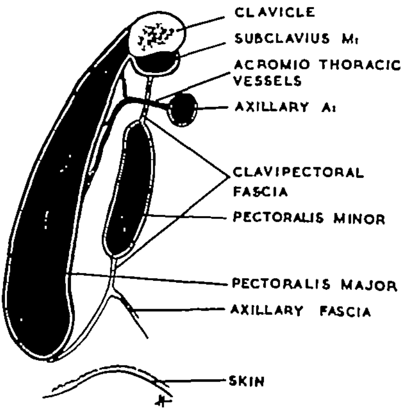

FIG 31 Diagram to show arrangement of the clavipectoral fascia

tail of the breast and the lymph nodes already described The interstices between these structures are filled with fibro-fatty tissue

The axillary neurovascular bundle runs from the apex of the axilla, along its superior angle, to the arm It contains the axillary artery and vein and the brachial plexus, all of which are bound together loosely inside a fibrous envelope The arrangement of the brachial plexus does not now concern us except for some of its branches The axillary vein which lies antero-inferiorly in the bundle is, however, of moment to the surgeon because it must be stripped of its fibro-fatty covering if the closely adjacent lymph nodes are to be removed The vein lies clear of the cords of the brachial plexus which are arranged round the artery

The vessels which arise from the axillary artery and vein in the axilla have already been enumerated Those which concern the surgeon doing a radical mastectomy are the superior thoracic, the acromio-thoracic, the lateral thoracic and the subscapular arteries and veins The nerves of importance leaving the neurovascular bundle in the axilla are the nerve (of Bell) which supplies Serratus anterior, the thoraco-dorsal nerve supplying Latissimus dorsi, the lower subscapular nerve to Subscapularis and the medial and lateral pectoral (anterior thoracic) nerves which supply the Pectoralis muscles

The nerve to Serratus anterior leaves the

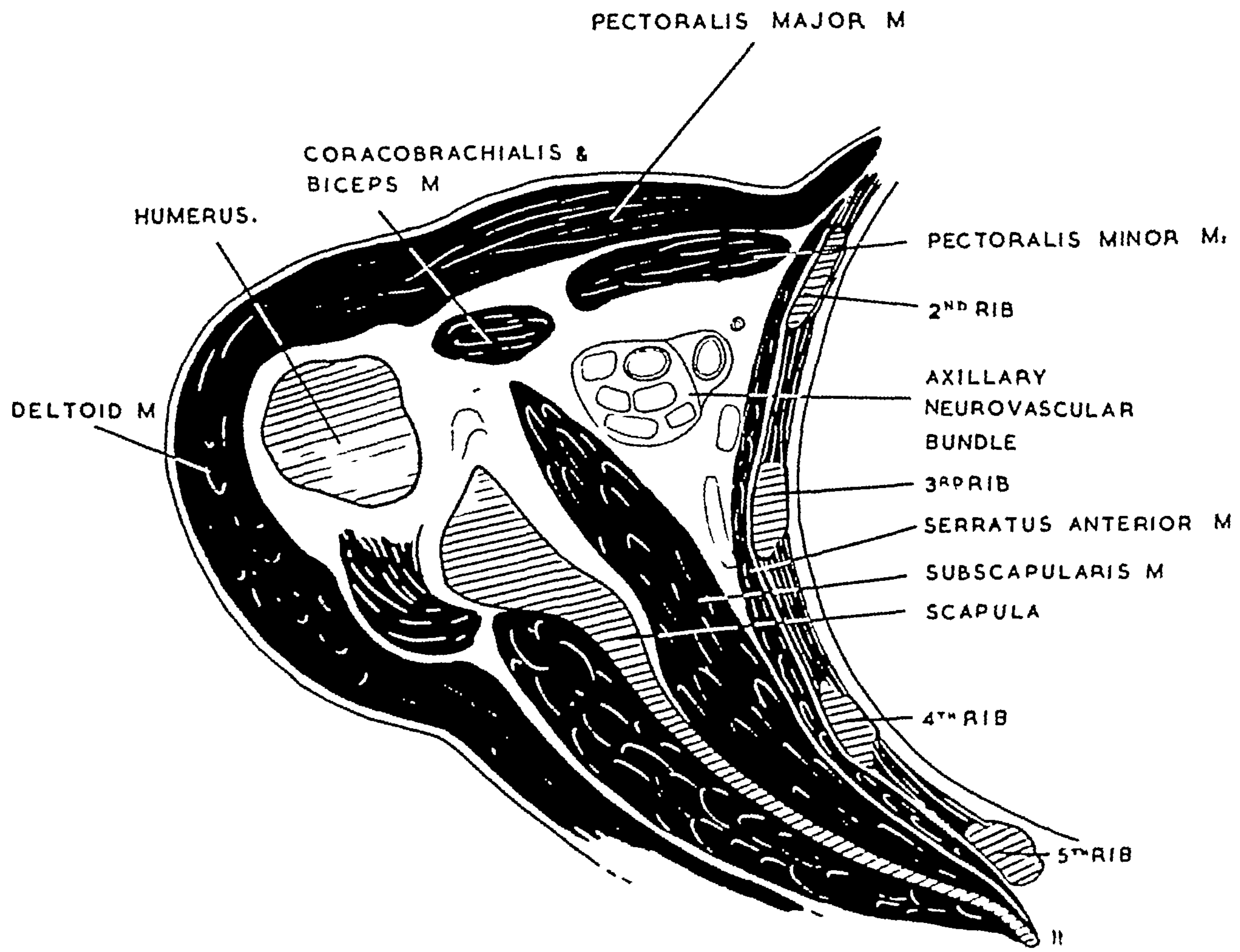

FIG. 32 Drawing of transverse section of the axilla, from a specimen in the Department of Anatomy of the Middlesex Hospital Medical School

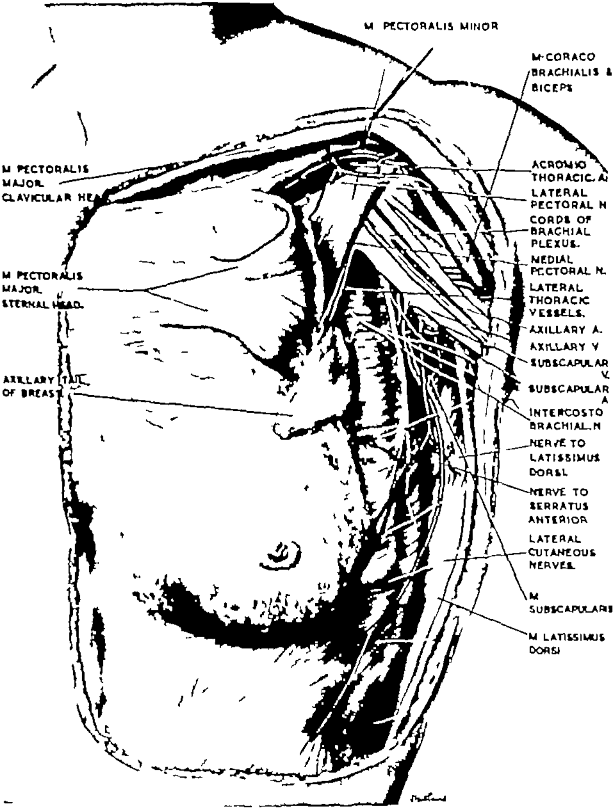

FIG 33 Dissection of the breast and axilla (from a dissection prepared by Dr J M Lancaster) The subscapular vessels in this cadaver lay anterior to the nerve to Latissimus dorsi

other chapters (XI, XII). The foregoing paragraphs merely indicate a few of the anatomical considerations which should illuminate such operations

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CHAPTER III

Physiology of the Breast

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Physiology of the Mammary Glands

It has long been recognized that the mammary glands form an integral part of the reproductive system in mammals Throughout life their activities are intimately associated with and dependent on, the endocrine pattern of the particular subject The natural sequence of pregnancy and lactation was obvious even to primitive man The same too applies to the phenomena of estrus in animals and menstruation in primates they are dramatic phenomena and their cyclic nature as a manifestation of sexual function was appreciated early It is only during the last 40 years dating from the pioneer observations of Loeb (1) in 1917 that attention has been focused on breast tissue as a sensitive index of endocrine function in health and disease The isolation of estrin by Allen and Doisy (2) in 1923 followed gradually by the discovery and synthesis of other sex hormones, gave the impetus to experimental work in this field Unfortunately from the standpoint of therapy scientific knowledge of endocrine secretions has outstripped the clinical practice of endocrinology the application of information gleaned from experiments on mice rats rabbits guinea pigs and ruminants has been a slow and frequently disappointing process The single fact of importance which emerges from the experimental field is that breast tissue though unessential to life is influenced by more hormones than any other organ in the body

Synopsis

The processes involved in breast development and function will be considered under the following headings

- I The role of the hypothalamus
- II The role of the endocrine glands
  - A The hypophysis
    - 1 Pituitary gonadotrophins
      - a Follicle-stimulating hormone (FSH)
      - b The luteinizing hormone (LH or ICSH)
    - 2 Prolactin also known as luteotrophin
  - B The gonadal hormones
    - 1 Estrogen
    - 2 Progesterone
    - 3 Androgen
  - C The placenta
  - D The adrenal cortex
  - E The thyroid gland
- III The role of the liver in steroid metabolism
  - A Normal liver function
  - B Liver disease

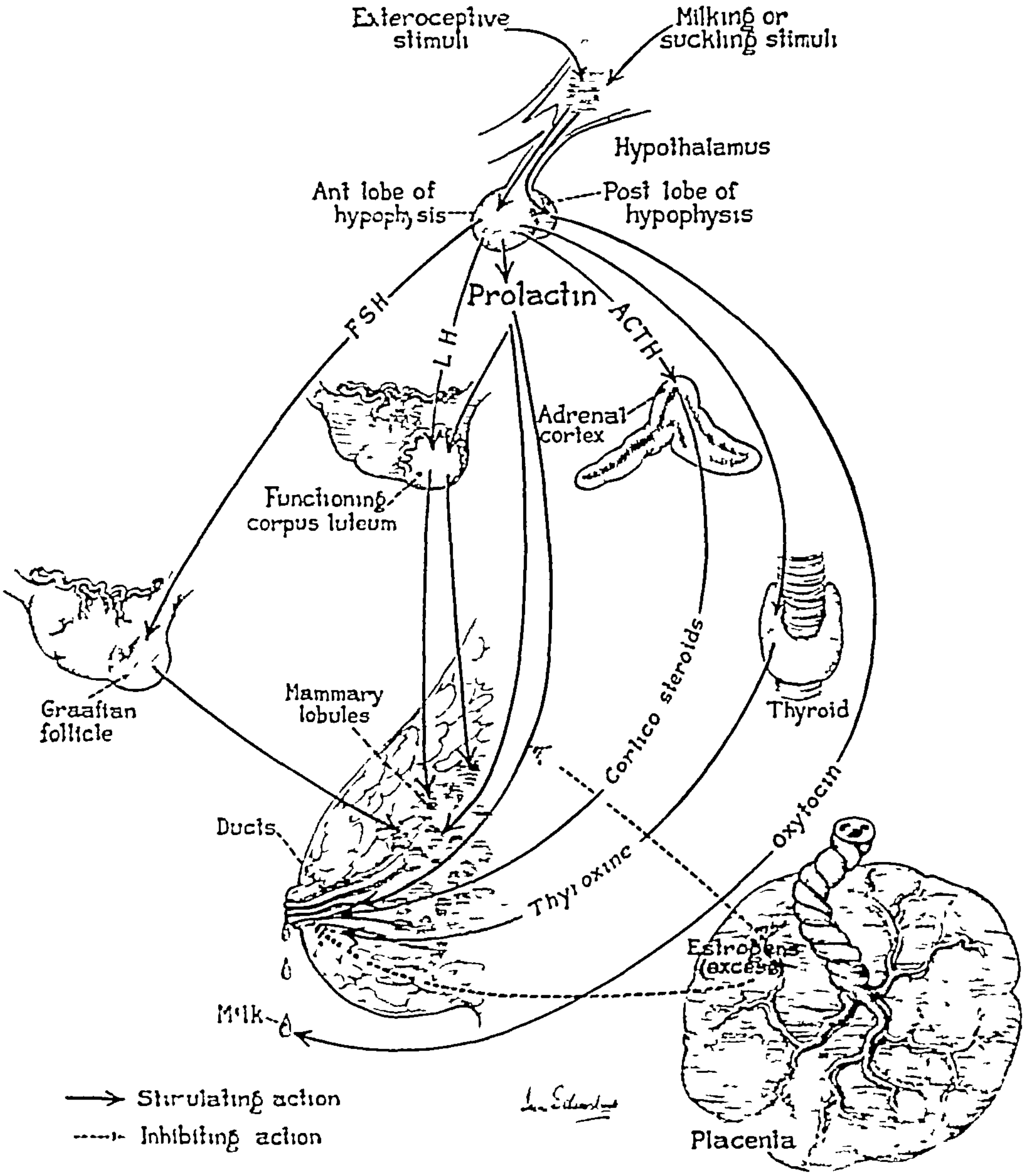

FIG. 36-A Schematic illustration of the interaction of the various hormones in regulating breast development and in the control of lactation

IV Nervous mechanisms
V Clinical considerations
- A Infancy
- B Childhood
- C Adolescence
  - 1 Female
  - 2 Male
- D Breast secretion
  - 1 Pregnancy
  - 2 Abnormal secretion
- E Post menopausal involution

The Role of the Hypothalamus

The traditional view of endocrine function has been to regard the hypophysis, or pituitary body, as "the conductor of the endocrine orchestra." Researches over the last decade, summarized by G W Harris (3) in 1951, have demonstrated that this role belongs to the hypothalamus, it is in this area that neural stimuli are integrated with humoral factors—for example, the level of circulating hormones in the blood The ac-

tual route of communication between the hypothalamus and the hypophysis is highly controversial but most observers agree that the hypophyseal portal blood vessels play a part in this mechanism

As yet knowledge of the function of the hypothalamus rests mainly on the circumstantial rather than factual evidence Some light has been shed by post-mortem findings in symptom complexes such as the Laurence-Biedl Moon syndrome The association of obesity and disturbances of sex functions is well known to clinicians as is the over eating associated with some emotional and psychopathic states The hypothalamus has been thought to play a part in the regulation of fat carbohydrate and water metabolism although animal experiments suggest that this may be secondary to its role in the regulation of appetite Closely related to the function of controlling food intake is that of the regulation of body temperature and energy exchange which has been investigated by Brobeck (4) It is also thought that in animals the control of certain primitive reactions associated with defence or attack is located in the hypothalamus It has been suggested that the hypothalamus may be the site of the sympathetic and parasympathetic centers In man the control of emotional states is thought to originate in this area as well as the control of the sleep rhythm and of genital functions In this regard the clinical observation that in emotional states there is frequently disturbance of the menstrual rhythm and even amenorrhea seems relevant Markee Sawyer and Hollinshead (5) have been able to demonstrate in experimental animals that the hypothalamus controls ovulation, with the resultant formation of a corpus luteum in response to release of LH They concluded from a series of experiments in rabbits that the central stimulus was adrenergic rather than cholinergic in nature, and originated in the hypothalamus They were able to demonstrate later (6) that this reflex could be blocked by the anti adrenergic drug Dibenamine and more recently have found this sequence to be preceded by a cholinergic stimulus, which could in its turn be blocked by intravenous atropine or by the administration of the anti cholinergic drug Banthine •

Hillarp (7) has attempted to define in rats the accurate localization of the hypothalamic centers associated with gonadotrophic functions earlier experiments had shown that damage to the median eminence of the hypothalamus inhibited the secretion of both FSH and LH with resultant atrophy of the gonads By using a special electrode he was able to inflict minimal damage in chosen areas and found that a state of constant estrus followed bilateral injuries lateral and caudal to the third ventricle extending from the optic chiasma to the mammillary bodies Hillarp concluded that the center for LH production was situated anterior and ventral to the paraventricular nucleus, with a system of associated fibers occupying the lateral aspects of the median eminence

The Roll of the Endocrine Glands

The Hypophysis

This gland is essential to life and in combination with the hypothalamus regulates the activities of the endocrine system Animal experiments have shown that pituitary deficiency leads to atrophy of the gonads and adrenals with subsequent breast involution and absence of function The active principles which govern gonadal activities are known as the gonadotrophic hormones and their production is a response to a delicate balance between the pituitary and the *gonads* Much of the early experimental work was performed by P E Smith (8), dating from as early as *1916 and led to the*

recognition of two distinct factors, now described as the follicle-stimulating hormone (FSH) and the luteinizing or interstitial-cell stimulating hormone (LH or ICSH) Subsequent investigations suggested that the effects of these two groups of hormones did not explain the whole story of ovarian function and Astwood (9) in 1941 demonstrated that prolactin through its luteotrophic properties actually was responsible for the formation of the corpus luteum hormone

A substance, similar in nature though different chemically from the pituitary gonadotrophins, was isolated from pregnancy urine by Zondek and Aschheim (10) in 1927 and designated as a prolan That this substance was placental in origin was confirmed experimentally by Seegar Jones, Gey and Gey, (11) when they succeeded in isolating gonadotrophins from a tissue culture of placental cells

The reciprocal relationships of the steroid hormones and the pituitary gland, with resultant cyclic activity, are somewhat complex Astwood (9) is of the opinion that both the pituitary and the ovary have an inherent rhythm and tendency to cyclic activity, and that the need for a regulating mechanism is minimal The experiments of Greep and Jones (12) have suggested that in the immature animal, the ovary exerts a restraining effect on the pituitary However, Marden (13) has shown recently that the ovarian restraint can be overcome by sufficiently high dosage of gonadotrophins, in that he was able to produce ovulation in calves one week old, using a sequence of anterior pituitary extract high in FSH, followed by chorionic gonadotrophin

Fevold (14) had demonstrated that both FSH and LH are necessary for the secretion of estrogen The effect of the estrogen is then to inhibit further release of FSH from the pituitary and to stimulate the liberation of LH and luteotrophin Small amounts of LH continue to be produced until the luteotrophin has effected the elaboration of large enough quantities of the corpus luteum hormone progesterone, to terminate this activity According to Astwood (9) the most important aspect of regulation is the suppression of LH formation, by the action of progesterone, he regards the action of estrogen on the pituitary as of secondary importance The titer of the ovarian hormones is by no means the only factor in gonadotrophin production Hormones from the other target glands, especially the thyroid, exert some influence Dietary and nervous factors are also important, as in chronic starvation or malnutrition This was observed frequently during the war years in occupied countries and in prisoner-of-war camps, when, in many of these women, sexual cycles gradually disappeared

The mechanism for the production of gonadal hormones would appear to be as follows The effect of the release of FSH in the female is to cause growth of the ovarian follicle beyond the stage of antrum formation, small amounts of LH are probably being secreted during the follicular phase, and when the LH:FSH ratio reaches a certain level, ovulation occurs In addition to stimulating further LH production by the pituitary, the effect of estrogen is to mobilize cholesterol and to cause its retention in the interstitium and theca interna cells of the ovary Everett (15) found that administration of LH led to ovulation in the absence of the hypophysis The actual amounts of cholesterol present in the ovaries can be assessed by the finding of so-called "Schultz-positive" material (oxycholesterol) MacKay and Robinson (16) examined a series of human ovaries and found a cyclic variation in the amounts present, which accorded with the findings on endometrial biopsy.

The deposition of cholesterol seems to depend on the LH/luteotrophin ratio Thus,

LH is responsible for the presence of the ground substance, and luteotrophin for its conversion into progesterone Greep and Jones (12) demonstrated that massive estrogen therapy in rats led to a state of pseudopregnancy FSH and LH were suppressed but not luteotrophin so large amounts of progesterone resulted

In the male, FSH has the effect of stimulating the epithelium of the seminiferous tubules to continuing production of spermatogonia and primary spermatocytes LH or ICSH, stimulates the interstitial cells to form androgens, and so influences the development of secondary sex characteristics This effect has been utilized by McArthur (17) in a biological test for the presence of LH or ICSH in human urine a non toxic concentrate is prepared and injected into an hypophysectomized rat The weight increase of the ventral lobe of the prostate forms an accurate index of LH activity

The gonadotrophins have been found to be either proteins or polypeptides they disappear very rapidly from the blood stream Their fate in the body is unknown but small quantities appear in the urine They are found in the urine first at about eleven years of age and are present in varying amount in both sexes throughout life After castration both FSH and LH continue to be secreted and stored in the pituitary Both have been demonstrated in human urine after gonadectomy and the natural menopause

The generally accepted theory of mammary development has been that once gonadotrophins are produced in significant amounts the gonadal hormones are responsible for subsequent changes by direct action An alternative theory suggested and supported by Turner and his associates (18 19) is that the gonadal hormones act only as pituitary stimulants—that Mammogen I, produced in response to estrogens leads to ductal development, and Mammogen II stimulated by estrogen and progesterone is responsible for lobulo-alveolar growth One clinical observation throws doubt on this theory—if estrogen is applied locally to the breast in an attempt to increase its size (frequently for cosmetic reasons) the other breast is unaffected, suggesting a local response unrelated to the pituitary Also Reece and Leathem (20) were able to produce mammary development in hypophysectomized rats by the combination of prolactin and estrogen Both Nelson (21) and Lyons (22) have produced experimental evidence which indicates that the three elements essential for mammary growth are the pituitary hormone prolactin, and the ovarian hormones estrogen and progesterone Lyons experiments were performed on normal animals and on those with various combinations of ablation of the gonads hypophysis and adrenals Prolactin appears to act as the mammary growth stimulating hormone Both of these observers demonstrated a substance similar to prolactin in the rat placenta, which they thought stimulated the production of progesterone and promoted lobulo-alveolar growth

Prolactin, or the lactogenic hormone, was discovered first by Stricker and Grueter (23) in 1928 and since then exhaustive studies into its properties have been made by Corner (24) Riddle (25), Gardner (26) Folley (27) and their associates Whereas originally it was thought to be solely connected with lactation, the diversity of its nomenclature suggests a broader field It is referred to also as luteotrophin and mammotrophin Nelson (28) suggests that its activities are varied with the demands of the body and are thus threefold—luteotrophic mammotrophic and lactogenic

The cyclic activities of luteotrophin in controlling progesterone production have

recognition of two distinct factors, now described as the follicle-stimulating hormone (FSH) and the luteinizing or interstitial-cell stimulating hormone (LH or ICSH). Subsequent investigations suggested that the effects of these two groups of hormones did not explain the whole story of ovarian function and Astwood (9) in 1941 demonstrated that prolactin through its luteotrophic properites actually was responsible for the formation of the corpus luteum hormone.

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been described earlier Undoubtedly, part of the mammogenic effect of prolactin is due to its luteotrophic action in forming progesterone However, Lyons (22) has shown that prolactin has a direct stimulating effect on mammary epithelium He observed local hyperplasia with mitoses, as well as the local initiation of lactation, following intraductal injection of prolactin Desclin (29), in an attempt to elucidate the relationship of prolactin and progesterone, treated two series of female rats with progesterone, one group had the ovaries intact, and the other was castrated Both were subjected to uterine trauma The intact group showed extensive lobulo-alveolar development, whereas the castrated group showed a lesser degree of development, but abundant alveolar secretion Desclin felt that the secretory processes were most marked in the absence of the ovaries and the resultant absence of luteotrophic demands

All observers agree that the initiation of lactation is entirely dependent on a healthy pituitary, but can only occur in breasts primed by estrogen Folley (30a, 30b) describes lactogenesis as being a response to the coordinated action of a complex of anterior pituitary hormones, centering around prolactin (lactogen) as an essential element He makes a distinction between the phenomena of lactogenesis and galactopoiesis, pointing out that crude anterior lobe extract is a more efficient galactogogue than purified prolactin Once lactation is established, the lactogen content of the pituitary remains high while nursing is maintained, this was demonstrated by Reece and Turner (31) in 1936 Hooker and Williams (32) were able to retard mammary involution by lactogen injections in the absence of nipple stimulation, thus demonstrating that suckling results in the release of prolactin

Various attempts have been made to account for the actual initiation of lactation Most theories seek to explain first why this phenomenon does not occur until after parturition, in spite of the continuous presence of prolactin The corpus luteum has been suggested as an inhibiting factor, but nursing has been observed to persist in spite of a subsequent pregnancy The injection of progesterone does not inhibit lactation The same arguments may be used to refute the idea that the presence of the placenta is a limiting factor Sometimes the placenta is retained in cows, yet lactation with adequate milk production ensues The experiments of Selye, Collip and Thompson (33) suggesting that the persistence of uterine distension acted as a deterrent were not confirmed in separate experiments by Bradbury (34) and Greene (35)

The most generally accepted idea is that lactation is kept in abeyance during pregnancy by high levels of circulating estrogens, which suppress the release of prolactin as well as inhibit its local action on the mammary glands Nelson (28) thinks this action is a direct one in opposing the lactation-inducing influence of prolactin A variant of this theory is the "double-threshold" theory put forward by Folley and Malpress (36) in 1947 They suggest that the high levels of estrogen in pregnancy inhibit prolactin release, whereas low levels stimulate the secretion of prolactin

A somewhat different view of the mechanism of the initiation of lactation is held by Petersen (37), who feels that the onset of lactation is more likely to be due to stimulating factors post-partum, rather than to the removal of inhibiting factors He points out that secretion is actually present before parturition, that the alveoli are distended late in pregnancy He suggests that it is the posterior pituitary which is responsible for converting lactation potential to milk production and that this effect is due to the oxytocin produced during parturition He

feels that subsequently, as a result of nursing oxytocin is produced by the posterior pituitary and leads to contraction of the muscle fibers in the breast, as a result milk flows from the alveoli into the ducts and sinuses As milk is withdrawn it is reformed provided nutritional requirements are adequate

Prolactin is found in the urine of infants even before nursing begins It may be derived from either the maternal or fetal pituitary the latter being stimulated by the sudden fall in blood estrogens The fact that some secretion may occur in the new born infant ("witchs milk") *suggests that the* fetal breast tissue has been subjected to the action of both pituitary and ovarian hormones in utero Lyons (38) states that two-thirds of all new born infants have mammary enlargement (see fig 178 A and B Chapt XX), and of these more than half secrete colostrum. Alveoli are seldom found in these immature breasts but Richardson (39) stresses the fact that fetal duct cells do have a limited capacity for secretion

The Gonadal Hormones

Gonadal hormones have been divided into three groups—the estrogens the androgens, and progesterone and all are necessary for the full development and functional capacity of the mature reproductive system Their mode of action is extremely complex, and there is considerable overlapping between hormones of these groups both with one another and with the hormones of the adrenal cortex All are sterol derivatives and are allied to cholesterol other related compounds are Vitamin D calciferol aglycones of the digitalis glucosides and certain carcinogenic agents such as methylcholanthrene The steroids are produced by tissue which originates in the celomic mesothelium—the ovary the testis and the adrenal cortex The widespread distribution of these steroids in nature would suggest that th are primitive growth regulators which ha acquired specialized functions in mamma Their function appears to be that of stim lating cell proliferation and differentiati in structures common to both sexes t embryonic Mullerian and Wollfian app ratus the nipples breasts and extern genitalia The action of these hormones organ rather than sex specific experimen work has shown that the capacity of a cell tissue to respond to a gonadal stimulus innate and survives transplantation

All three types of gonadal hormones produced *by both sexes and it is possil* that steroid hormones are interconvertal in vivo Indeed as Frank (40) has said ' permanent condition of chemical hermaph ditism persists throughout life in the hum male and female" Cooperation betwe these hormones is essential to the well-bei of the sexual organs small quantities estrogens being essential to the male a androgens in the female Males are mo sensitive than females to estrogen stimu tion and females to androgen effects O explanation of this difference in sensitiv may be that prolonged exposure to one pa ticular hormone leads to an adaptation the part of a particular individual Howev Steinach and Holzknecht (41) were able demonstrate by replacing ovary by tes in female guinea pigs that growth exceed that of the normal male and that in the verse experiment in a male littermate bod growth was less than the normal fema Lipschutz and Tutso (42) made observatio on the breasts of castrated male and fem guinea pigs into which ovaries had be grafted and found more rapid enlargeme of nipples and mammae in the male anim All three hormones given in sufficient qua tities can suppress ovulation temporarily the female, estrogen and androgen will cau atrophy of the gonads in both sexes on pr

was found by Greep and Jones (42) to have no appreciable effect in this regard

The existence of two separate ovarian hormones was first demonstated by Marshall and Jolly (43) in 1905 They found in dog experiments that the administration of an extract of estral ovaries could produce estrus, whereas corpora lutea had a separate effect Twenty years elapsed before the two groups were isolated by chemical and biological methods, and once purified extracts were obtained, experimental advance became possible

The Estrogens. The estrus-producing hormone was first isolated from the ovary by Allen and Doisy (2) in 1923, and from pregnancy urine by Aschheim and Zondek (44) in 1928 The hormone was later prepared in pure crystalline form and three separate chemical compounds found to exist —estradiol, which is probably the actual form of estrogen secreted by the ovary, estrone and estriol, which are less potent and may represent oxidation products produced in the liver Like all hormones, estrogens disappear rapidly from the blood stream and are not stored in appreciable quantities in the body They appear in the urine in small amounts in childhood, increase from about the age of eight years onwards, and several months before the menarche occur in cyclic fashion

Estrogen is the growth hormone of the female reproductive system, and so is responsible for the appearance of secondary sexual characteristics the feminine contours of the body and the enlargement of the breasts Estrogen, acting through the pituitary, stimulates the release of ACTH which results in the appearance of axillary and pubic hair It also promotes growth of the primary sex organs The feminine distribution of fat, the skeletal changes of puberty, and the pigmentary changes of pregnancy suggest its influence in the metabolism of fat, carbohydrate and protein, as well as that of minerals and pigment in the body

Bullough (45) has investigated the mode of action of estrogens in a lengthy series of experiments and has decided that the prime function is to stimulate mitosis throughout the body Such changes can be regarded as normal in the immature animal at puberty, they are essential to development and are permanent When estrogens are given to the mature animal, the changes are for the most part reversible One outstanding feature of mammary epithelium is its extreme sensitivity to hormone stimulation In this regard dosage is of the utmost importance Whereas small doses of estrogen lead to ductal proliferation, Gardner (46) demonstrated that large doses in most experimental animals lead to stunting and cessation of growth It has been found possible to produce some well-recognized pathological entities of the breast in experimental animals using injections of estrogen in varying dose schedules Goormaghtigh and Amerlinck (47), and later Geschickter, Lewis and Hartman (48), demonstrated the development of changes identical with those of chronic cystic mastitis, in experimental animals, by the prolonged use of estrogens Many brilliant contributions in this experimental field have been made by Cori (49), Lacassagne (50), Nelson (51), Gardner (52), Burrows (53) and others in an attempt to ascertain just what determines the borderline between the hormonal environment of normal growth and that required by tumorigenesis

At birth, the mammary gland in both sexes is about five millimeters in diameter and consists of relatively few branching ducts, which have originated from the invaginated ectoderm of the milk line The only change to occur in the prepubertal phase is the progressive growth of the ducts

Once the supply of estrogen becomes steady, as happens at puberty, extensive duct proliferation occurs with club-shaped swelling of the terminal ducts Dilatation of the ducts may occur as a normal process An increase in peri-ductal stroma may occur at this stage but according to Ingleby (54) connective tissue is always well developed in young breasts with early differentiation of peri-ductal and peri lobular tissue Connective tissue increase may become disproportionate in one area and lead to the formation of a fibroma or fibro-adenoma. Estrogens have been found also to cause enlargement of the nipples and pigmentation of the areola, changes that are particularly noticeable in pregnancy when estrogen levels are high due to placental estrogen production

Opinions are divided as to the extent of breast changes which are thought to accompany the menstrual cycle Loeb and Hesselberg (1) in 1917 found evidence of three distinct breast phases in the guinea pig as related to events of the sexual cycle Rosenburg (55) in 1922 reported examinations of a series of human breasts and decided that a physiological hypertrophy occurred in the premenstrual phase with abundant ductal outgrowth resulting in the formation of acini and lobules Involution with complete regression followed the onset of menstruation Moszkowicz (56) was more impressed by connective tissue changes than by those in the mammary epithelium Taylor (57) attempted to shed some light on this confused problem by examining tissue which appeared normal from patients undergoing breast surgery The only consistent change appeared to him to be in the individual epithelial cells, the outline becoming more distinct and the acini larger and more dilated he found no evidence of mitosis nor of desquamation It would seem that excessive importance may have been attached to the occurrence of cyclic changes and that as stated by Engel (58), differences of opinion in this matter are based on individual variations in anatomy, he states that in mammary glands containing a reasonable number of well-developed glands there is alveolar sprouting in the premenstrual phase, in breasts with scanty glands the menstrual response is slight All observers emphasized the lack of uniformity in glandular development of the breast

An interesting recent sidelight into this problem has been shed by the investigations of Pickles (59) into the variations of mammary blood flow These changes were estimated by a thermometric method and found to exhibit a cyclic pattern with maximal values in the luteal phase

Attempts to associate mammary disorders with abnormal estrogen stimulation or response have been inconclusive Estimations of urinary estrogens have failed to yield constant findings in patients with benign breast disease A recent attempt at hormone assay of breast tissue itself has been carried out by Kier Hickey, Keettel and Womack (60) They devised a method of detecting and separating estrogenic and androgenic substances by the use of ultraviolet light They found no increase in estrogens in patients with benign breast disease but a decrease in androgenic substances presumably progesterone The work is interesting but the results inconclusive as individual breasts react differently to hormonal stimuli in addition to the well known fact that there is inequality of response to the same hormone in a single breast However this direct approach is highly commendable

Progesterone Progesterone is the hormone of the corpus luteum and is concerned with the functions of conception gestation and possibly lactation In chemical structure this hormone resembles the hormones formed by the testis and adrenal cortex indeed in experimental animals it has been found pos-

sible to maintain life with progesterone following adrenalectomy. Corner and Allen (61) in 1929 were the first investigators to make a clinically effective luteal extract from the ovary, and, shortly after this, progesterone was isolated by several groups of workers. In addition to the fact that they may be produced in the adrenal and testis, progesterone compounds are elaborated in sufficient quantities by the placenta to compensate for the removal of the corpus luteum. Browne, Venning and Henry (62) found that there is an alteration in output between the seventieth and ninetieth days of gestation, indicating that the placenta takes over progesterone production at this juncture, which is a critical period in gestation. Progesterone is converted to pregnanediol in the liver, where it is subsequently conjugated with glycuronic acid for urinary excretion. It first appears in the urine within 24–48 hours of ovulation, disappearing about two days before menstruation. Only 10–20 per cent of administered progesterone is recovered from human urine. The pregnanediol level is not thought to be an entirely reliable gauge of progesterone metabolism.

The relative roles of estrogens and progesterone in breast development differ so in experimental animals that it is difficult to draw analogies with the human breast. In the mouse, rat and rabbit, estrogen leads to duct proliferation only. In the guinea pig, estrogen stimulation leads to growth of both ducts and alveoli, and lactation may ensue. However, it is quite possible that in the latter animal estrogen administration may lead to increased adrenal function, with a resultant increase in progesterone, either directly or indirectly as a by-product of desoxycorticosterone metabolism. Chamorro (63) points out that the same synergism exercised by estrogen and progesterone can be obtained by other steroids having a similar action, such as desoxycorticosterone or testosterone. Due to their known capacity as milk produ ruminants have been used extensively o experimental basis by Folley and assoc (64) and Mixner and Turner (65). I groups feel that although enlargement o mammary gland and ultimate secretio produced by estrogen, the glands are r normal histologically when progesteron combined in a suitable ratio. Folley thin is possible that in man estrogen can proc some alveolar development. A small s of adolescent girls was investigated Ingleby (54), who demonstrated the abs of alveoli before the menarche. Most servers are agreed that the formation of veoli and lobules commences at pub when progesterone first appears, and t the breast gradually assumes its adult str ture, culminating in the formation of tween 14 and 20 lobules situated clockw in the periphery of the gland. If pregna ensues, large quantities of progesterone formed by the corpus luteum, and the p centa and breast hypertrophy is a fa early manifestation, especially in primipa. Secretion does not occur for several mont. An irregular hyperplasia occurs of both e thelial and connective tissue elements, Da son (66) has stated that the first evidence budding of alveoli occurs around the ten week. The first half of pregnancy is occup by the development of ducts, lobules a alveoli. Early in pregnancy the connecti tissue exhibits marked cellularity, but la on it is obliterated by the growth and a tivity of the glandular elements. Once lact tion is established the breast morpholo becomes uniform, and secretion is wid spread, although groups of acini will displ different degrees of activity. After pre nancy, involution occurs in much the sa haphazard manner as growth occurred wi generalized atrophy of both epithelial a connective tissue elements, however, o or both elements may persist in some area

Androgens The prime function of androgens is to stimulate the development and maintenance of the male sex characteristics. Thus androgens act as the growth hormone of the maturing male and at adolescence in addition to growth of the penis, scrotum, prostate and seminal vesicles, gradual changes occur in the musculature skeletal system and larynx as well as in the skin and in the appearance of pubic facial and axillary hair Androgens also play a more general part in the body economy, they promote nitrogen anabolism and influence electrolyte and water metabolism to the extent of causing retention of sodium chloride ions potassium and phosphorus These elements are essential for protoplasmic growth Androgens seem to promote cell growth generally and the growth spurt of adolescence in both sexes may well be due to the hormones of the testis and adrenals It is doubtful if androgens are produced normally in the ovaries.

The determination of the chemical nature of the androgens followed the isolation of an androgenic substance by McGee (67) in 1927 and later it was found possible to synthesize various androgens from cholesterol and bile acids. The most powerful androgen is testosterone which has been isolated from the testes of bulls Human androgens are excreted in the liver as neutral 17 ketosteroids as are synthetic androgens Testosterone is apparently converted in the liver to the less potent androgens androsterone and its isomer aetiocholane Androgenic compounds are excreted in the urine by both sexes throughout life The urine of a female contains about half the quantity of androgenic substance of male urine All urine contains several androgenic compounds and it is difficult to separate the adrenocortical and testicular steroids Urinary 17 ketosteroids can merely be regarded as a broad index of adrenocortical and male gonadal activity

There is no reason to believe that androgens act normally on breast tissue so any effects described have been observed under experimental conditions It has been found that in embryos androgens can retard and even suppress the development of the nipple In post-natal life the effect is reversed and hypertrophy of the nipples occurs This is a direct effect and independent of the pituitary and the ovary Experimental observations on the action of androgens on the breast parenchyma have produced variable and confusing results Undoubtedly the effect depends on the dosage the type of androgen used the species and maturity of the experimental animal and the pre-existence of formed breast elements In moderate amounts androgens do stimulate the mamma, but only in animals characterized by some degree of breast development normally Chamorro (63) points out that while both testosterone and progesterone stimulate the breast, the latter has the power of 'feminizing' the breast which testosterone can never do Testosterone merely develops pre-existing ducts and acini

Experimentally it has been found possible to carry breast development through to lactation by means of androgens G L Laqueur (68) was able to induce a state of pseudo-pregnancy in young adult virgin rats by the use of testosterone provided the treatment was started in estrus These animals were able to nurse young in response to the suckling stimulus

Androgens have been used clinically to suppress lactation In 1938 Kurzrok and O'Connell (69) reported a series of women treated successfully with testosterone propionate

The suggestion has been made that there is a second testicular hormone, which is thought to be analagous to estrogen and is

referred to as "inhibin", or the x-hormone The absence of this hormone was suggested by Klinefelter, Reifenstein and Albright (70) to explain the triad of signs referred to as the "Klinefelter syndrome"—gynecomastia, aspermatogenesis without aleydigism, and an increased urinary excretion of FSH The gynecomastia was attributed to the action of androgen in the absence of inhibin If one accepts the evidence of Warren (71) and Maddock (72) that estrogen production occurs in the Leydig cells, it is difficult to believe that the gynecomastia was not estrogenic in origin

The Placenta

Experimental work has suggested that the placenta can maintain mammary development after hypophysectomy Desclin (73) was able to demonstrate a normal sequence of mammary development in pregnant guinea pigs following hypophysectomy He found that atrophy occurred following removal of the pituitary in male guinea pigs in which mammary development had proceeded to the colostrogenic stage under estrogen therapy

Leonard (74) studied mammary development in rats by removing in turn the hypophysis, the ovaries, the fetuses and the placenta, and found that the placenta was the essential factor Lyons (22) has shown that the rat placenta contains a substance identical with prolactin, in producing luteotrophic and mammotrophic effects The placenta apparently plays an important role in mammary development by stimulating the production of progesterone

Hisaw (75) demonstrated that chorionic gonadotrophin was able to prolong luteal function in the monkey, this was confirmed in the human by Bradbury, Brown and Gray (76) It seems probable that a state of synergism exists between luteotrophin and chorionic gonadotrophin

The Adrenal Cortex

Perhaps the outstanding physiological advance of the last two decades has been the investigation of the adrenal cortex, which began with the isolation of Kendall's (77, 78) compound E in 1935 and culminated in the clinical experiments of Hench (79), reported in 1949, using the substance now known as cortisone, in the treatment of collagen diseases An additional stimulus in the experimental field had been given by the report in 1942 that 11-oxysteroids were being used on the Luftwaffe pilots to postpone fatigue, Kendall had shown that cortical substances made rats resistant to strain and to cold, as well as to certain poisons

Next to the pituitary, the adrenal is perhaps the most complex of the endocrine glands and produces a variety of hormones which are essential to life and to sexual functions Like the other ductless glands, it is subservient to the pituitary by means of a "check-and-balance mechanism," its activities being regulated by the adrenocorticotrophic hormone (ACTH) The adreno-cortical hormones themselves influence gonadotrophin production and sexual abnormalities have been observed to accompany tumors of cortical tissue

Three main groups of cortical hormones are recognized and attempts have been made to correlate their function and origin with the three distinct cell zones of the cortex However, it seems possible to make only the general statement that the mineralocorticoids, which regulate the metabolism of water, sodium and potassium, and the glucocorticoids (including cortisone), which aid in carbohydrate, fat and protein metabolism, originate in the periphery of the gland The miscellaneous group classed as "X" hormones, which include the sex steroids and the cortical elements associated with sex hair growth, are produced near the medulla

All of these hormones are steroids and although their metabolism is unknown, they are probably modified in the liver and appear in the urine as steroid end products Recent techniques have made possible the separation of 17 ketosteroids, androgenic substances, and *reducing corticoids*

There is considerable overlapping in the activities of the hormones of the adrenals and the gonads The adrenal is a known source of estrogens androgens and progesterone the later being most closely allied in structure and function to the adreno-cortical hormones In some experimental animals it was found possible to induce progestational changes in the uterus with desoxycorticosterone acetate

There is clinical evidence that estrogens are still produced in the body following castration or the menopause their origin being the adrenal gland Novak and Richardson (80) reported on a series of endometrial biopsies in postmenopausal women and found evidence of a virtual continuance of ovarian function Cyclic vaginal bleeding has been observed in young women castrated for breast carcinoma. Huggins and his co-workers (81, 82) have suggested that in younger patients there is increased function of the adrenal cortex following castration, with resultant outpouring of steroids This is the rationale of their combination of bilateral adrenalectomy with castration in the treatment of breast carcinoma by this method the excretion of estrogens is abolished entirely

In experimental animals it has been found possible to produce mammary development in the absence of gonads This was demonstrated by Cowie and Folley (83) in 1944 they removed the gonads from a series of both male and female rats and later removed the adrenals from certain animals All animals were given a series of injections of ox pituitary extract and later killed Those animals without adrenals showed no breast changes, whereas the remaining animals showed marked mammary development, greater in the females. Gynecomastia has been observed in patients with certain types of adrenal tumors as well as following the *administration of ACTH* Adrenosterone and corticosterone will both cause enlargement of the nipple

Although adreno-cortical hormones do not act as lactogens, as measured by the pigeon's crop gland method without them lactation is a failure The mechanism was investigated by Nelson and Gaunt (84) in a series of experiments and found to be a factor of the role of the adrenal in the metabolism of salt and water

The Thyroid Gland

The observation that widespread bodily changes accompany thyroid disorders dates back to the time of Hippocrates when the goiter was treated with the ash of sponges, to combat iodine deficiency French investigators during the last century inquired into the problems of endemic goiter and subsequently the thyroid gland was proved to contain iodine The chemistry of the active principle called thyroxin was elucidated by the experiments of Kendall (85 86) from 1915–1919 Later this compound was synthesized and found to be derived from the amino-acid tyrosine in union with iodine the hormone is stored in the gland as thyreoglobulin and released by a proteolytic enzyme. The thyroid hormone can be estimated in the blood as serum protein bound iodine and is possibly utilized in the tissues as triodothyrine Production of this hormone is regulated by the thyrotropic hormone of the pituitary

Although the thyroid hormone is not essential to life profound changes occur in its absence Kendall (85) has suggested that thyroxine controls the mechanism per

mitting maximum flexibility of energy output Cell metabolism is directly proportionate to the amount of circulating hormone Normal body growth and maturation of the skeleton do not occur in diminished thyroid function The thyroid hormone has been observed to increase the bodily demands for vitamins, minerals and water It is intimately bound, too, with the metabolism of the steroids, in that it influences fat metabolism, by acting to decrease the fatty acids, cholesterol and phospholipids in the serum

Estrogen has been found to antagonize thyroid function by inhibiting the production of thyrotropin Menstrual disorders frequently accompany thyroid dysfunction Every clinician is aware that the more or less empiric administration of thyroid extract to patients with an unexplained sterility will sometimes result in pregnancy This result is not limited to patients with an elevated blood cholesterol

Animal experiments to determine the part played by the thyroid in mammary growth have shown varying degrees of exuberance in the absence of this gland Nelson and Hickman (87) in 1937 reported marked mammary development in normal and castrated rats subjected to thyroidectomy Leonard and Reece (88) conducted a similar experiment, giving estrogens to the two groups The mammary glands of the castrated group showed extensive ductal development, with lateral and end buds, those animals combining thyroidectomy with estrogen therapy showed copious ducts and alveoli The control animals, castrated and treated by thyroidectomy, showed an advanced degree of development Apparently both an excess and deficiency of thyroid substance favor mammary growth Chamorro (63) has observed a condition resembling chronic cystic mastitis in female rats rendered mildly hypothyroid, by the use of propyl-thiouracil He has produced similar changes in castrated female animals treated with testosterone proprionate, after being rendered hypothyroid In these animals the uterine mucosa also presented a cystic hyperplasia Chamorro feels that the thyroid hormone exerts a specific protective influence on breast tissue against harmful steroid effects and that this harmful effect may be exaggerated when there is a decrease in thyroid function

Deviation from normal thyroid function has been found to impair lactation, lactation can occur in the absence of the thyroid gland, but the amount and duration are lessened The effect of thyroid administration in lactation has been investigated in cows by several groups of workers, with the consistent finding that it is ineffectual in augmenting an otherwise satisfactory lactation, but that when the yield is declining an increase by as much as 30 per cent can be attained (89) Overdosage can cause undesirable loss of weight The results of thyroid administration in hypogalactia in humans have not been encouraging, although Robinson (90) in 1947 reported a series of 126 cases treated by a combination of crude ox-pituitary and four grams of thyroid extract daily, twice as many women were still able to breast feed their infants at six months as in a control series Some elevation of pulse rate occurred, but no evidence of thyrotoxicosis

The Roll of the Liver in Steroid Metabolism –

Normal Liver Function

The study of hepatic physiology can rightly be said to have originated in the classical experiments of Claude Bernard (91, 92) in Paris, published a century ago His spiritual heir was F C Mann of the Mayo Clinic, who pioneered many experimental techniques in this field Zondek (93) in 1934 suggested that inactivation of steroids took place in the liver Since then the

association of liver disorders with hormonal imbalance has been widely studied

The liver is the largest and most important gland in the body Its functions are many and varied, but may be classified briefly as follows metabolic pigmentary, secretory, excretory, detoxicating and hemopoietic In recent years experiments have shown that the liver plays a vital part in water metabolism water balance is apparently controlled by the relation between the diuretic effect of the adreno-cortical hormones and the anti diuretic hormone of the posterior pituitary This latter hormone is inactivated in the liver and in liver dysfunction the normal antagonism between the two hormones is disturbed This work was reviewed by Gaunt Birnie and Eversole (94) in 1949 and by Birnie (95) in 1952

From the point of view of steroid and fat metabolism there appear to be two key substances in the liver—cholesterol and choline The former is a complex hydro-aromatic secondary alcohol which is an essential com ponent of all tissues Its presence in bile and its migrations in the gastro-intestinal tract are well known but apart from these activi ties it is possible that cholesterol may be the mother substance of the bile acids the estrogens the progesterones and the male sex hormones Choline appears to be essential for normal liver function especially fat metabolism It is a vasodilator and occurs in combination as acetylcholine it also forms part of the molecule of the phospholipids lecithin and sphyngomyelin Another vital factor in steroid metabolism is folic acid one of the vitamin B complex Apparently it is essential for the exercise of the tissue growth function of estrogens. Hertz (96) in 1948 investigated the growth of the genital tract of the chicken and demonstrated that folic acid was essential for maximal response The degree of response could be altered by varying the proportion of folic acid in the diet Similar experiments have been carried out in monkeys and frogs. Hertz (97) has since demonstrated that the response of the oviduct to estrogen can be inhibited by ad ministering the folic acid antagonist ami nopterin No such dependence on folic acid appears to exist in the male It is possible that this estrogen folic acid link may be related to the sex difference in the red cell count, and to the macrocytic anemia which develops in pregnancy and responds to folic acid

Animal experiments proved early that estrogens given by injection disappeared rapidly from the blood stream Only about 10 per cent is recoverable from the urine. As stated earlier Zondek was the first to put forward the hypothesis of liver inactivation and this has been established beyond doubt by subsequent experimenters. Heller (98) in 1940 demonstrated the inactivation of estradiol by liver slices in vitro About 80 per cent of the estrogen delivered to the liver is rendered non-estrogenic, this change is thought to occur in the hepatic cells and is enzymatic in nature The major part of the estrogen undergoes an enterohepatic circula tion similar to that of the bile salts When estrogen leaves the liver it is bound to a protein and is inactive however a rapid con version to a dialyzable form occurs as needed with the aid of β-glucuronidase It had formerly been thought that conjugation with glucuronic acid occurred in the liver as a detoxicating process prior to excretion Now it seems that this process, described by Fishman (99) as metabolic conjugation' is an essential one in the utilization of estrogen by the tissues.

The liver is the chief site of androgen alter ation resulting in the urinary excretion of compounds of lowered potency It has been shown that administration of testosterone in man leads to an increase both of androgens and estrogens in the urine androgen can be

converted to an estrogen in the body, probably estrone

The metabolism of the adrenocortical steroids is not clear It is presumed that a similar process occurs in the liver as in metabolism of the sex steroids Burrill and Greene (100) found a diminution in potency of desoxycorticosterone tablets implanted in the mesentery and hence subjected to early liver action Adrenal steroids appear in the urine as 17-ketosteroids and are thought to comprise from two-thirds to three-quarters of the total ketosteroids

Liver Disease

Experimental work has shown that the liver has an enormous safety margin, due to an ample reserve capacity, and extraordinary powers of regeneration Inflammatory, toxic or circulatory changes must be widespread in the liver before clinical evidence is available of disturbed steroid metabolism The latter may not occur until some stress has disturbed the equilibrium of a "compensated cirrhosis" It is thought that cirrhosis of the liver is on the increase, due to the epidemics of acute infectious hepatitis in World War II, to sulfonamides, aureomycin and other hepatotoxic agents and to homologous serum jaundice

The association of gross liver disease with breast manifestations was investigated by Glass, Edmondson and Soll (101, 102) in 1939–40 They correlated their findings with two earlier groups in the literature, and referred to the combination of atrophic cirrhosis, ascites, testicular atrophy and gynecomastia as the "Sylvestrini-Corda syndrome" In these cases large amounts of free estrogen were found in the urine Bennett (103) has reported a series of autopsies of patients dying of cirrhosis of the liver, in which consistent changes were found of testicular atrophy, metaplasia of the prostatic epithelium and hyperplasia of breast tissue

In 1946, Gilder and Hoagland (104) presented a careful study of eleven male patients with acute infectious hepatitis. At the onset of the disease urinary estrogens were found to be high, and 17-ketosteroids low This latter level returned to normal before the estrogens Dohan, Richardson, Bluemle and Gyorgy (105) studied a series of patients with liver disease, and found a high total estrogen excretion, associated with less than average gonadotrophins and 17-ketosteroids The men with stable or advancing gynecomastia had a much higher level of estrogen excretion than those without gynecomastia or than the controls

The length of time taken for these changes to appear is emphasized by the report of Hibbs (106) of 500 cases of gynecomastia in men who were prisoners of war of the Japanese Most of these men suffered from malnutrition with attendant vitamin deficiencies, amebic and bacillary dysentery and malaria Gynecomastia did not appear for an average of 18 months after capture

Zondek and Black (107) in 1947 attempted to assess liver dysfunction in disease by means of an estrone clearance test. They performed liver function tests and estrone clearance tests on a series of controls, a group of pregnant women with infectious hepatitis, and a group of patients with cirrhosis These workers found that even extensive liver disease was not associated with an increased endogenous estrone level in the blood nor in the urine However, the clearance of exogenous estrone was markedly delayed in severe cases of infectious hepatitis, characterized by a loss of ability to synthetize urea In some moribund patients the ability to inactivate estrogens outlasted urea production In cirrhosis of the liver, the increased values of estrone clearance paralleled the clinical deterioration and could be used as a prognostic sign

Nervous Mechanisms

Every clinician is familiar with the thin nervous woman with the painful nodular breast and the frequent association of sterility and dysmenorrhea a sufferer from the so-called "premenstrual tension syn drome. Emotional stress has been observed in excitable subjects to result in breast symptoms. Psychic factors such as stimulation of the nipple as a sexual practice, have been reported as leading to prolonged nipple secretion in the absence of pregnancy Breast enlargement has been observed in pseudocyesis

Attempts at understanding the influence of the vegetative and autonomic nervous systems on mammary function are based almost solely on animal experiments The efferent fibers are relatively unimportant, as lactation has been found to occur both after section of the spinal cord and after transplantation of the mammary glands to abnormal sites The required stimulus is provided by prolactin in the blood stream The initiation and maintenance of lactation are dependent on afferent impulses to the central nervous system, with the resultant discharge of prolactin Selye Collip and Thomsen (33) investigated the sequence of weaning and involution of the breast, secretion continued in spite of milk accumula tion while suckling was permitted using an obstructed nipple

The sympathetic nervous system appears to have some control of the trophic functions of the breast Ernst (quoted by Taylor) (57) contributed a series of animal experi ments based apparently on clinical observa tions and found that removal of the thoracic ganglia as far as T_3 resulted in breast atrophy with the disappearance of functional elements. Cannon and Bright (108) in 1931 observed a reduction in milk supply and loss of maternal instinct in animals subjected to sympathectomy Occasional cases have been observed of unilateral breast atrophy patients with chronic phthisis, which may due to an intrathoracic nerve injury

Clinical Considerations

Infancy

The earliest manifestations of the ser tivity of breast tissue to hormonal stimu tion may occur in either sex during the fi two weeks of life Swelling of the brea occurs frequently, associated at times w milky secretions In the female, slight va nal bleeding may also occur from a hyp plastic endometrium but this subsides the congested uterus decreases in size Th changes subside slowly and it is usua three to four months before the organs ha returned to normal The infantile bre consists merely of a disc-shaped areola s mounted by a papilla

Childhood

Normally the breast retains the infant contour until somewhere between the ter and fourteenth years Pryor (109) examin 100 normal girls and found that budding the breasts occurred anywhere between 1(and 14 7 years By this time the deposition fat and the effect of hormonal stimulati causes the breast to assume the so-call 'bud outline The areola is elevated a forms with the papilla a small conical p tuberance Occasionally this degree of (velopment becomes apparent before the a of eight years when a condition of sex precocity is said to exist Other evidences genital maturation may also be present a represent either a true precocious puberty a pseudo-precocious puberty Tumors of t hypothalamus ovary and adrenal glands a rare and must be eliminated in the diff ential diagnosis. Most cases of female p cocity belong in the group classed as ' cc stitutional," whereby sexual developme proceeds in normal sequence but at an

tonishingly early age, Novak (110) has reported a case with the menarche at fifteen months

Sometimes one group of target organs will respond more readily to minute doses of circulating estrogens Talbot, Sobel, McArthur and Crawford (111a) have observed a series of children from two years of age upwards, with the sexual immaturity consistent with their chronological age, yet with varying degrees of mammary development These children show no appreciable change in urinary hormones Breast enlargment has been observed also during estrogen therapy for gonorrheal vaginitis The condition recedes when therapy ceases

Adolescence—Female

The breast changes of adolescence proceed in unison with the change in body stature Usually at puberty the breast has assumed the primary mamma shape, which has been described as a "truncated cone situated on the summit of a flattened hillock "

The age at which sexual development becomes manifest is influenced by genetic factors The average age of the first menstrual period is 13 5 years (112) The menarche is usually followed by menstrual irregularity, and it is approximately three years before a normal menstrual rhythm is established Ovulation, which is marked by the appearance of pregnanediol in the urine, occurs usually around 14–15 years of age (111b)

Usually both breasts develop at the same rate, but occasionally one will become much larger than the other Rarely, a diffuse virginal hypertrophy will develop and may be unilateral or bilateral The breasts become enormous, a condition which may regress spontaneously, but more often persists and may necessitate operation for psychological reasons

Cheatle (113) described a "puberty mastitis" occurring between the ages of 10 and 14 years The condition is frequently bilateral, and a painful hard disc-shaped swelling appears beneath the areola This condition usually undergoes spontaneous regression and was attributed by Cheatle to an accentuation of physiological hypertrophy of the peri-canalicular and peri-acinous connective tissue A similar condition has been observed in males

Adolescence—Male

The male mammary gland does not undergo the gradual enlargement described above as occurring in the female In boys it is abnormal for signs of sexual maturation to appear before the eleventh year, and the first changes usually involve the testes, penis and scrotum A moderate degree of breast enlargement has been found to occur in a large number of normal boys—a condition classed as simple adolescent gynecomastia The condition may involve one or both breasts, and usually subsides in about two years If the condition is bilateral and persists for several years, the existence of a Klinefelter syndrome should be suspected

Gynecomastia is probably due to an excess of estrogen, an increase in the estradiol-testosterone ratio, or else an undue susceptibility of the tissues to the effects of estrogen (see Chapter XX)

Geschickter (48) was able to demonstrate the development of gynecomastia in male monkeys by the use of estrogens The direct effect of estrogen therapy has been observed in humans in the treatment of transvestitism (114) where estrogen produces gynecomastia and testicular atrophy, the former frequently follows estrogen therapy in prostatic carcinoma Gynecomastia may occur at any age and may be easily explained by its association with testicular atrophy or neoplasm, or liver dysfunctions, or with certain characteristic tumors such as teratomata,

hypernephromata or adreno-cortical tumors However, in many cases the etiology is obscure

Breast Secretion

Pregnancy The mammary glands can not be regarded as having attained full development until pregnancy has occurred followed by a period of lactation During pregnancy the breasts undergo a true hypertrophy, involving all tissue elements Occasionally a gross and almost pathological enlargment occurs, associated with constitutional symptoms.

Breast enlargement is accompanied by more superficial changes prominence and pigmentation of the nipple and areola, the appearance of Montgomery's tubercles and of a secondary areola Veins become prominent and striae are frequently visible. Some secretion can be expressed from the nipple by the sixth month.

Once lactation has subsided, involution of the breast occurs, but the virginal state is never regained The breast now has the contour of maturity the areola having receded into the breast tissue and the papilla only projecting If abnormal involution occurs there may be scattered areas of hyperplasia in ducts and acini associated with desquamation resulting in diffuse and painful induration

Abnormal Secretion It is not uncommon to have a milky secretion persist for several years in the breasts of multiparae following full lactation The presence of a milky fluid may sometimes be demonstrated in women who have never been pregnant. A rare condition occurs in which lactation persists for several years following delivery it is associated with amenorrhea, and thought to be due to a pituitary disorder This is known as the Chiari syndrome Argonz and del Castillo (115) have reported a somewhat similar combination of symptoms thought to be due to hormonal imbalance, in which hypoestrogenism and galactorrhea are associated with a low FSH

Post Menopausal Involution of the Breast

There is no sudden change in the breasts at the menopause, whether natural or surgical The contour of the breast may actually alter very little as fat deposition replaces tissue lost by atrophy Some women may complain of transient breast pains and scattered areas of tenderness Certainly periodic examinations are important at this time, even in the absence of symptoms, as the peak incidence of breast carcinoma is in the early fifties (see Chapter XIX)

Microscopically, there is a gradual and irregular alteration of breast architecture which may antedate the menopause by many years in multiparae Geschickter (116) showed that 33 per cent of women dying between the ages of 30 and 40 years already manifested lobular irregularities in the breasts Early changes include epithelial proliferation with dilatation and coalescence of alveoli to form minute cavities Later on there is shrinkage and disappearance of the alveoli and a resultant destruction of the lobular pattern As the epithelial elements regress the stroma becomes denser due to a blending of the various connective tissue elements, the periductal, the intra lobular and the inter lobar tissues Sometimes the histological picture may become confused by underlying traces of incomplete involution if pregnancy and lactation have occurred in middle life

In a small group of senile women the histological picture may be one of extreme epithelial proliferation Several layers of cells may appear and the epithelium be thrown into folds but without any breach of the ductal or alveolar confines Traces of the larger milk ducts can frequently be found surrounded by a large amount of elastic

tissue In a series of supposedly normal breasts examined post mortem by Frantz and associates (117) approximately half the patients over sixty years of age had dilated nipple ducts

It is most unlikely that senile involution leads to complete extinction of mammary tissue, nor does the breast tissue ever lose its sensitivity to estrogen stimulation Recent evidence on this point has been provided by Huseby and Thomas (118) who examined the apparently normal breasts of patients about to commence estrogen therapy for unilateral breast carcinoma They found that most of these breasts contained evidence of residual lobules The effect of treatment was to reverse the normal processes of breast atrophy, though the resultant picture was not that of a pre-menopausal breast Not only was there widespread evidence of epithelial proliferation, but in some patients lobules appeared resembling those of pregnancy It is seldom, however, that a patient comments on breast enlargement during hormone therapy

Summary

At attempt has been made to review the biochemistry and general physiology of the endocrine secretions, with particular reference to their effects on the breast

The chief characteristic of breast tissue would appear to be its extreme sensitivity to hormonal stimulation The endocrine relationships responsible for normal breast development and function are complex and involve most of the endocrine system, under the influence of the hypothalamus and the hypophysis

The pituitary hormone prolactin appears to be the dominant factor in breast physiology It is thought to act as the growth hormone of the mammary glands and to direct the activities of the gonadal hormones It exerts a luteotrophic action in promoting the secretion of progesterone Finally, it is established beyond doubt that prolactin is the hormone of lactation, although the actual mechanism whereby prolactin overcomes the antagonism of estrogen to initiate secretion is unknown

Estrogen has been shown to promote growth of the ductal system in normal development, and progesterone of the lobulo-alveolar elements

The liver plays an essential role in the metabolism of steroid hormones Inactivation undoubtedly occurs in this organ, and in addition the formation of inactive protein-bound estrogen, which can be converted into a physiologically active form as needed, by the action of glucuronidase It has been suggested that folic acid is essential for estrogen utilization by the tissues

Gross disturbance of liver function is frequently associated with gynecomastia in males, but there is no similar breast sign of liver dysfunction in females

It has been found possible to reproduce various pathological entities in experimental animals by varying estrogen administration However, no constant pattern of estrogen excretion has occurred in subjects with breast disorders

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CHAPTER IV

Experimental Aspects of Mammary Cancer in Mice

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Introduction

The primary function of investigations on cancer in experimental animals in addition to the fundamental data which may be obtained should be that of assisting in the understanding and the eventual control of the problem in humans That such a realization has not been obtained is obvious to all However, it is recognized that the control of cancer need not be dependent upon the comprehension of all basic data as shown by the ability to alleviate other diseases

Following the investigations of scores of workers using inbred strains of mice which represent the closest approach in biological material to pure chemicals the complexity of the cancer problem is becoming more evident Also it is probable that there are still many ' pieces yet to be demonstrated as part of the mammary cancer puzzle in mice only one of the many types of cancer Each is an enigma in itself with many of the parts not interchangeable

That mammary cancer in mice is not a single disease should be obvious from this discussion Thus, the causative factor(s) for the genesis of one type may or may not be necessary for the development of another type" in these experimental animals and differences may exist in the histologic appearance of these tumors or they may be indistinguishable

No attempt will be made in this report on experimental mammary cancer in mice to give a general review of the subject for many have been published during the past few years (11 32 50 55 57 60 88 92 108 118 152) and references will be found in these publications for many subjects not considered extensively here It is the intention of the writer to indicate what information will have to be obtained to ascertain if the same causative factors might operate in mice and men in the genesis of mammary cancer Without such information it would be difficult to state that a factor might not be active in individuals of the two species

Previous to 1933 it was assumed that spontaneous mammary cancer in mice resulted from two primary causes inherited susceptibility and hormonal stimulation (152) when almost concurrently the Staff of the Jackson Memorial Laboratory (135) and Korteweg (144) reported that another factor maternal in nature also was responsible for the development of these tumors.

In these studies reciprocal crosses were made between mice of inbred strains having

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either high or low incidences of mammary cancer When the maternal parents were representatives of strains with high incidences, many of the first generation (F_1) progeny also had mammary cancer, when the offspring were obtained from the reciprocal crosses, low incidences were observed These data demonstrated that the mothers of the cancerous strains had contributed some "influence" which was not, in these experiments, transferred by the paternal parents of these stocks

Such an influence could be transferred from mother-to-offspring by any of the following (a) cytoplasmic transmission, (b) during intrauterine development, and/or (c) via the mother's milk

In 1936 (37) the first report was made regarding the influence of nursing upon the genesis of mammary cancer in mice In this experiment, *offspring born to females* of a cancerous strain were transferred, soon after birth, to foster mothers of a strain with a low incidence of spontaneous mammary cancer Most of the fostered mice of the cancerous strain remained free of the disease, as did their progeny and descendants, although mice of only one generation were fostered Representatives of the 18th–35th generation descendants of one of the first females of the A strain to be fostered, and observed between 1943–1948, were found to have an incidence for breeding females of 0 3 per cent (63)

On the other hand, if mice of the same litter are permitted to nurse their mother for the same time before they are fostered, different results may be obtained One female may die noncancerous and have progeny and descendants with a low incidence, another may die noncancerous yet have cancerous offspring, and a third may develop mammary cancer and have cancerous progeny (37) Caesarian section is a more effective method of eliminating the agent that is transferred in the mother's milk than is foster nursing However, the latter technique shows that mice of the same litter may give variable results, that some may become infected while others may not, and a delay of 24 hours prior to fostering may have little effect in reducing the incidence of mammary cancer

This mammary tumor agent, abbreviated to MTA, has the properties of an infectious agent or virus Cytoplasmic (145, 166, 167) and intrauterine (99) transfer of some maternal influence for mammary cancer in mice have been suggested as possibilities, but neither theory has been supported by critical experimental data

Following the testing of reciprocal hybrids, nursed by females of the two maternal strains with high and low incidences, and observed either as virgins or breeders, a *theory was suggested that mammary cancer in mice usually resulted from the interaction* of three primary causes 1) the mammary tumor agent, 2) inherited susceptibility and 3) hormonal stimulation (38, 39, 50) In general, if any one of these causative factors is lacking, a low incidence will result In advancing this hypothesis, it was recognized (46, 50) that mammary cancer developed in a few mice of most strains, and some appeared in animals considered to be nonsusceptible and which did not possess the MTA

Genetics

Investigations on the mammary tumor agent have altered some of the original concepts regarding cancerous and noncancerous strains of mice, and of susceptibility vs nonsusceptibility to spontaneous mammary cancer Further studies also have demonstrated that other physiological mechanisms are of great significance, the effects of which are controlled, directly or indirectly, through genic action

In the cross between females of the cancerous dilute brown and males of the yellow strain, Little (149) found that a higher percentage of the non yellow mice had mammary cancer than did those with yellow coat color Linkage was not indicated since similar results were seen in mice of both the F_1 and F_2 generations

An analysis of the reproductive histories of the females showed that the yellow mice passed through their breeding period sooner than did the non yellows and it was concluded (149) that this physiological factor probably resulted in a lowered hormonal stimulation of the mammary glands and consequently, a lower incidence of mammary tumors in the yellow mice However, when the yellow mice did become cancerous, their average cancer age was found to be three to four months earlier than was noted for the cancerous non yellow mice

Later Kasten (137) reported that some effects of the yellow gene are mediated through metabolic dysfunctions involving the endocrine system There was increased food intake producing obesity which disrupted ovarian function causing sterility

The role of the inherited susceptibility to the development of mammary cancer as transmitted by one stock (38 39 49 54) may be summarized as follows (54)

Reciprocal F_1 hybrids produced by mating mice of one low cancer (C57 black or B) and one high cancer (A) strain and nursed by females of the cancerous strain gave in breeding females approximately the same incidence of spontaneous mammary cancer

No evidence was secured to suggest an intrauterine influence for the development of mammary cancer in mice.

The incidence in the total number of F_1 hybrids nursed by females of the A stock did not differ significantly from the incidence secured in mice of the cancerous A stock.

'Although the pooled data obtained in all the hybrid generations could be accounted for on the genetic theory that the inherited susceptibility for mammary cancer in this cross was transmitted as a single dominant factor it becomes evident on analysis of the incidence of cancer in the several subgroups that such a simple interpretation is inadequate and that other factors are probably involved Detailed analysis shows

1 That the incidence of mammary carcinoma in the F_2 hybrids with brown coat color was significantly higher than in their litter mates with black or albino coats

2 That not all brown mice became cancerous nor was the incidence in brown mice as high as in mice of the high cancerous A stock

3 The progeny of brown mothers had a higher incidence than did the progeny of black or albino mothers but not all brown mothers transmitted the inherited susceptibility to their progeny

'4 The incidence of cancer was significantly greater in some groups in the mice born in the third and later litters than in mice born in the earlier litters from the same mothers

5 The incidence in the progeny was influenced also by the age at which the mothers developed mammary cancer

It has previously been shown that a considerable proportion of mice of one so-called nonsusceptible stock developed mammary cancer when given the active milk agent Therefore even mice of these strains are not totally resistant and either they must possess certain factors conducive to mammary carcinoma production or the tumors must result from extrinsic and/or metabolic inciting influences Obviously the mice of low cancer strains do not have all the inciting factors that are present in mice of the high cancer strains

"If some mice of a genetically nonsusceptible strain develop mammary cancer, it is probable that some cancerous hybrid animals are likewise nonsusceptible. Thus, the incidence would not represent the true percentage of susceptible animals, and should not serve as the only basis for a genetic interpretation of the data."

"It is concluded that the inherited susceptibility for spontaneous mammary cancer in mice, as transmitted by mice of the cancerous A stock, probably depends upon multiple genetic factors, one of which may be linked with the gene for brown coat color."

The influence of the litter in which the young were born and the age of the mother at the time mammary cancer appeared, seen in this particular cross, has not been encountered in other crosses.

An effect of the agouti coat-color gene upon the development of mammary cancer was observed by Heston and Deringer (121), with the non-agouti mice having a lower incidence.

Others (167) concluded that the tendency to develop mammary cancer was not inherited, with the extrachromosomal influence, now called the mammary tumor agent, being the primary inciting factor.

Possible effects of genes in controlling other physiological processes have been indicated in many investigations, and these will be considered under specific topics.

The Mammary Tumor Agent (MTA)

Distribution of the MTA

It was determined soon after the demonstration of the MTA that extracts of tissues from infected mice would produce mammary cancer if given to young susceptible animals which did not previously possess the agent. The material containing the agent may be given orally (47) or by subcutaneous, intraperitoneal (40) and intracerebral (55) injections. Following administration, the agent may be transferred in the milk of the injected females, even though they may die noncancerous (40).

The MTA has been shown to be widely distributed in the body of the host, as determined in the following studies: grafts of thymus, mammary glands (40), spleens (24, 40), extracts of lactating mammary glands (43, 196), spontaneous mammary cancer (16, 52), liver (57, 58, 85), stomach milk from young mice (85, 125), whole blood (212), including serum and resuspended cells (56), etc. Following the grafting of spleens from infected mice, the agent could be recovered from the spleens of the injected mice within a period of three weeks (176). Seminal vesicles (17) and the sperm from the cauda epididymis (160) of males of cancerous strains also were found to be cancer-inducing.

Early tests (43) of the liver gave negative results, and others (113) were unable to demonstrate the agent in whole blood or blood fractions.

In one study the agent could not be recovered from the embryo and placenta (125), and while others have also failed to show the presence of the agent in embryos from females of cancerous stocks (85, 164), their test animals injected with extracts of the placenta did develop mammary tumors (85, 164). Muhlbock et al. (164) were able to produce tumors in mice following the administration of extracts of tumors, blood, and spleen from pregnant females at term as well as from nonpregnant females. Hummel and Little (126, 127) had previously reported negative results using tissues obtained from pregnant females at term.

Following the transplantation of mammary tumors into mice which did not carry the agent, the MTA has been recovered in the extracts of such tumors after ten (59, 66, 69, 126), 30 (66), and 12

(84) passages In several of these experiments, tumors were assayed which developed in fostered mice of the C57 black stock, and the agent was found to survive for ten (59 66) and 42 (84) passages

The agent has been found to retain its tumor inducing properties following lyophilization (47) filtration (16 50 52) treatment with glycerin (16 48), desiccation (55 82) even after storage for two years (82) treatment with petroleum ether and acetone, and at pH values between 5 0 and 10.2 (31 33) Inactivation of the agent occurs at a temperature of 56°C for 30 minutes (16 31)

In determining the most satisfactory source material for biological and chemical studies on the MTA several factors are of great importance Based upon the results obtained by reciprocal crosses between cancerous strains, the agents from the two parental strains may not show the same tumor producing activity in the reciprocal F_1 hybrids or in mice having the same genetic constitutions (36 42 60 71, 168) Thus in assaying for the agent from different sources the test animals should bear the same genetic relationship to the donor stocks and multiple tests should be made because of the variation between the tissues of different mice of the same stocks

For studies where large amounts of tissues may be needed especially when the experiment covers a period of several days, transplanted mammary cancer may be the most satisfactory source of the MTA (66)

For the biological assay of extracts for the MTA young animals should be injected for it has been demonstrated (4 10 24 50 51 55 64 83 88 92) that when mice older than three to four months of age are used lower incidences are obtained In one experiment (83) this age resistance was overcome by the repeated injections of large amounts of material containing the agent in another, the old mice which received the most concentrated fraction in multiple doses showed as did their progeny, the lowest incidence of mammary cancer (64)

These data may be comparable to that obtained following male transmission of the MTA regarding the sensitivity of the stock to the development of mammary cancer We have found (68) that females of the C strain which show the highest incidence following mating with males having the MTA may be the most susceptible to the development of tumors when older mice are used In a group of nineteen which received the amount of the agent from 10^{-3} gm equivalents of mammary cancer and injected between the age of 100 and 120 days, eight have developed mammary cancer and seven are still under observation in litter mates which were injected with 10^{-1} gm equiv per dose for five injections two of twenty have had mammary cancer

That the age factor may not be due to the greater development of the mammary glands at the time of administration of the agent was investigated by the use of castrated males bearing grafted ovaries (130) In one group the males were gonadectomized and ovaries were grafted when the animals were one month of age followed by the injection of the agent The incidence in this group was 74 per cent the average cancer age was 10.5 months Two other groups of males castrated at one month, were treated as follows In one group ovaries were transplanted when the mice were one month of age but the agent containing extract was not injected until the mice were four months of age in mice of the other series ovaries were grafted at the same time the agent was injected namely at four months The incidences in these two groups were 27 per cent and 24 per cent respectively The latent period

two had mammary cancer, but of their 22 progeny born in their fourth and succeeding litters, 19 died cancerous at an average age of 288 days

Three C57 black *females of different* litters, but all representatives of the generation nursed by Z females, also were tested by using Zb males Of their 39 F_1 progeny, 92 per cent had mammary cancer The average cancer age for the entire group was 291 days, or by mothers, from 281 to 302 days The three noncancerous hybrids were members of either the first or second litters and lived to an average age of 688 days, the 11 cancerous females of these litters had their tumors at an average age of 356 days

The observations reported here, using mice of the same subline of the C57 black stock, are quite different from those reported by Andervont (8), and may result from using females of different sublines of the same cancerous stock as foster mothers Such data may indicate that mice with the same genetic constitution may not propagate and transmit the "agents" from different cancerous stocks with the same effectiveness The litter in which the offspring were born also influenced the incidence and average cancer age in the progeny, this was noted especially when they were susceptible to spontaneous mammary cancer

In another subline of the C57 black stock, Dmochowski (89) has found an incidence of mammary cancer of approximately 18 per cent No mouse of the stock has ever been nursed by a female of a cancerous strain, but biological assays of the tumors have demonstrated that they possessed the mammary tumor agent The agent has been transferred in the stock for at least ten generations, although, in some pedigrees, mammary tumors were absent for five or six generations When mice of the same line of C57 black stock were fostered by females of the cancerous RIII strain, the incidence of mammary cancer was found to be about 15 per cent

The origin of the MTA in this subline of low cancerous mice is not known, but it has been found to occur in other instances (44, 51, 60, 63), when in mice of a susceptible stock, a high incidence of mammary cancer was observed in the succeeding generations (44)

Mice of the I stock, with a low incidence of mammary cancer, have been tested by Andervont (2, 6) and the author (65) to determine their susceptibility and ability to propagate and transfer the MTA Again, different cancerous strains were used as foster mothers

Andervont (2, 6) found that of the 47 females of the I strain nursed by females of his cancerous C3H strain, two developed mammary cancer Eleven fostered I females, nursed by females of our A and Z (C3H) cancerous strains, and 42 of their descendants of the next two generations were found to remain free of mammary cancer (65)

Two of the I females which obtained the agent from the A strain were mated with a Zb male Of their 19 F_1 progeny, one had mammary cancer Three other I females, members of the same litter and nursed by a Z female, also were mated with a Zb male The incidences of mammary cancer in their F_1 progeny, by mothers, were 10, 25, and 83 per cent Those with the highest incidence showed an average cancer age of 242 days, for the others it was 343 days *Fifteen fostered I females* of the second and third generations, descended from mice nursed by Z females, were tested for the transmission of the agent by using susceptible Zb males An incidence of two per cent was found in their 131 F_1 progeny (65)

The development of mammary cancer in wild mice has been investigated by Andervont (15) In 20 wild mice fostered by

females of the cancerous C3H stock and their 71 descendants ten or 11 per cent had tumors, as compared with one of 36 of the unfostered group Females of the wild stock were used to nurse young mice of the C strain of which 25 mice or 57 per cent, had mammary cancer By observing these and other domestic mice for five generations after fostering by the wild females Andervont concluded that while the MTA from inbred strains induced few mammary tumors in the wild mice the results suggested that females of the wild stock carried an agent which would cause the disease in mice of inbred strains

In summary, it may be stated that these observations on the propagation and transmission of the MTA by mice of strains showing low incidences of spontaneous mammary cancer may not be accounted for by any one theory

Armstrong and Ham (25) tested extracts of mouse carcinomas which had been grown in chick embryos for 31 passages and found that the agent could be demonstrated

In another investigation Ambruse and Harrisson (1) used as their test animals young rabbits guinea pigs hamsters rats peromyscus and fostered C3H mice for assays of the tumor-inducing activity of an extract of a mouse mammary carcinoma None of the injected animals, except the C3H mice which had been free of the agent before treatment developed mammary cancer Some of the injected rats were used as foster mothers for fostered C3H mice but these fostered mice remained noncancerous, showing that the agent was not transferred in the milk of the rats

Chemical and Physical Properties of the MTA

Antibodies against the mammary tumor agent can be elicited in rabbits by injection of either crude or partially purified extracts of mouse tumors, and Andervont and Bryan (16) showed that the immune serum would neutralize the agent in in vitro and in vivo studies These observations have been confirmed although the serum produced against normal tissues of mice without the agent did not protect the animals in passive immunity studies (114) Likewise, the injection of anti-cancer serum into young mice of the cancerous C3H stock did not prevent the subsequent development of spontaneous mammary cancer (58)

Antisera from either rabbits or guinea pigs produced against either normal or cancerous tissues containing the MTA, will, in certain instances, neutralize and convey passive immunity against the agent (with Imagawa unpublished) Preliminary data from other experiments indicate that an antigenic difference may exist between the immune sera produced against the agent from different sources Numerous publications (34 92, 110 115 116 134, 155 156) have considered the use of immunochemical methods to detect the presence or absence of the agent in mouse tissues However (88) there is a similarity in the serological behavior of material prepared against normal and cancerous tissues with and without the agent and obtained from mice possessing comparable genetic constitutions

Comprehensive programs have been undertaken in several laboratories attempting to purify the MTA to study its chemistry, to observe it in the electron microscope, etc and numerous publications have appeared (30–33 77 111 112 129 136 171–173 197) including review papers (32 88 92)

In certain experiments it was determined based upon biological assay that the supernatant was essentially free of activity following centrifugation at a speed of

23,000 × G for 90 minutes (32, 33, 129), while in other studies the results indicated that the active particles were not sedimented until subjected to a centrifugal field of 120,000 × G for two hours (171–173)

Different methods were employed for the preparation of the tissue fractions Also, comparable studies were not made on the same strain of cancerous animals, and the variation of the size of the particles, as determined by sedimentation speed and electron microscopy, could have been due to the study of agents with different tumor-inducing activities Various results have been obtained in serial titration experiments in regard to the incidence of mammary cancer found in the test animals relative to the amount of material administered (14, 30, 32, 60, 64, 66, 112, 129)

Mammary Tumors in Hybrid Mice, Including Male Transmission of the Agent

Several investigators have reported that after males of cancerous strains, possessing the MTA, were mated with females free of the agent, higher incidences of mammary cancer were observed in the progeny than might have been expected In several instances, the agent was demonstrated in the spontaneous mammary tumors which developed in the progeny and the mothers

High incidences (over 50 per cent in some groups) were observed in the F_1 hybrids derived by mating females of the C strain with males of the cancerous C3H stock by Andervont and Dunn (9, 12, 17, 19, 22) When males without the agent of the fostered C3H stock were employed, or where an incidence of three per cent was found in breeders at 22 months (17), an incidence was found in the F_1 hybrids in one study (22) which was not significantly lower than when males with the agent were used

It had been demonstrated by Andervont (8) that females of the C stock would have a high incidence of mammary cancer when they possessed the MTA, obtained by nursing females of the cancerous C3H strain, yet not more than five per cent of the C females mated with C3H males developed mammary cancer The agent could not be demonstrated in many of the mammary tumors which developed in the F_1 hybrids of the C ♀ × C3H ♂ cross, except in a few hybrids which had tumors when they were from four to six months of age (12)

Several possibilities were considered and investigated by Andervont and Dunn (12, 13, 19, 21, 22) to account for the development of the mammary tumors in the hybrids Contamination appeared improbable as a method of transmission of the agent, for this would be expected to occur with the same frequency in other crosses and inbred stocks Suggestive evidence for the transmission of the agent by males of the cancerous stock was possible in some groups, yet when C females were mated with C males, after they had been bred with C3H males with the agent, their progeny showed a low incidence If the embryos became infected in utero, certain results obtained in these studies, as well as those published by others, might be explained Another possibility was that the agent could be attenuated, either before or after it entered the embryo, this would account for the development of tumors in very old mice If the activity of the agent was increased or a variant resulted, this would explain the appearance of tumors in young animals

To ascertain if females of the C stock might transfer an agent to their progeny which became more infectious in the hybrids, Andervont and Dunn subjected the C females to X-radiation (21) and increased

hormonal stimulation by using stilbestrol pellets (13) No increase in the incidence of mammary tumors was seen Consideration was given to the possibility that the agent might appear de novo (19), but evidence for this could be obtained only by eliminating the other theories

It was stated that on occasion the embryos might become infected in utero (21 22) but Muhlbock (164) was unable to confirm this and we have not observed any supporting data for such a theory

In 1949 Foulds (101) reported that when females of the C57 black stock with a low incidence were mated with males of the susceptible R3 strain without the agent few of their progeny had cancer but when males with the agent were used 15 per cent of the progeny died cancerous He observed a significant increase of tumors among the descendants of certain females descended from males which had the agent, and tests revealed the presence of the MTA in some of the tumors Foulds interpreted his results as due to the erratic transmission of the agent by the males of the cancerous stock This theory has been accepted and confirmed by others (13 22 61 63 87 160 163)

In their latest publication Andervont and Dunn (22) used 24 females of the C stock to obtain hybrids by mating them with agent-carrying or agent free males of their C3H stock None of the C females developed mammary cancer

To date (61 63 68) 41 females of the C stock have been crossed with males of our C3H line called the Z stock with the MTA In all five different groups were observed consisting of from five to 17 C females in each the incidence of mammary cancer in the C females varied from 50 to 60 per cent, with a mean incidence of 56 1 per cent

In our studies as well as that reported by Muhlbock (163) the females were permitted to bear as many litters as they would before they developed mammary cancer or died noncancerous In this respect the method of breeding differed from that employed by Andervont and Dunn as in their series of experiments few of the females were allowed to have more than four litters In certain experiments some progeny were mated from as many litters as possible in others few offspring were continued and these were usually from the later litters Table 2 presents data which are representative of several groups obtained by crossing C females with males of our Z (C3H) line with the MTA

The three cancerous C females averaged eight litters before they gave rise to mammary cancer at an average age of 558 days while the two noncancerous C females died at 664 and 402 days after having nine and seven litters, respectively

The time when the C females became infected with the agent from the male varied from mouse to mouse but by observing the development of mammary cancer in the CZF$_1$ progeny and correlating it with the cancer ages it is believed that the approximate time of infection can be determined As seen in the table, females also may become infected transfer the agent to their progeny in the milk yet die noncancerous.

In the early litters born to the C females or before they became infected five or 11 per cent of their CZF$_1$ hybrids were observed to develop mammary cancer The youngest hybrid mouse of the group to have cancer was 511 days and the average cancer age was 556 days (table 2) The cancerous C females became infected by the time they had three or four litters, and in this study both noncancerous C females also transferred the agent to their progeny one to offspring born in her fourth litter

TABLE 2

Occurrence of mammary cancer in C females and their CZF_1 progeny, obtained by mating C females with Z (C3H) males possessing the MTA

(C females + or − with age = age at appearance of cancer or death of noncancerous females, with the number of litters born to each female being given in brackets The CZF_1 progeny are listed by litters cancer/noncancer)

C Females	Litter in Which the CZF_1 Progeny Were Born								Mammary Cancer in the F_1 Hybrids, before and after Their Mothers Became Infected with the MTA from the Male	
	1	2	3	4	5	6	7	8	Before infection	After infection
+520 (8)	0/2	0/5	4/0	1/0	3/0	1/0	—	—	0/7	9/0
+493 (7)	0/4	—	1/3	4/0	1/0	2/0	—	—	1/7	7/0
+662 (9)	0/2	0/3	3/0	2/1	3/0	4/0	—	5/0	0/5	17/1
−664 (9)	—	1/2	1/2	1/4	—	0/6	0/3	3/1	3/17	3/1
−402 (7)	0/2	1/4	—	3/0	5/0	4/0	—	—	1/6	12/0
Total F_1 progeny									5/42	48/2
Per cent cancer									11	96
Average cancer age									556	242
Average noncancer age									692	497

the other to young of her eighth litter After the C females became infected with the MTA from the C3H males, 48, or 96 per cent, of their CZF_1 progeny gave rise to mammary cancer at the average age of 242 days The average cancer age for the offspring of the cancerous C females was 246 days compared with 235 days for the fifteen cancerous progeny of the noncancerous C females Before the C females became infected, their offspring had an average of 6 6 litters, but the cancerous hybrids born to the C females after infection averaged 4 0 litters

Several mammary tumors, from either C females or their CZF_1 progeny, were assayed and found to contain the MTA (61, 63). Muhlbock (163) also found more tumors in the hybrids born in the later litters, and a few tumors, of mice from early litters, did not carry the agent

Five C females, litter mates of those mated with males of the cancerous Z line (table 2), were crossed with Zb males (Z males without the MTA (51)) These C females survived to an average of 727 days, each had nine to eleven litters, and all died without mammary cancer Many of their $CZbF_1$ (C♀ × Zb♂) progeny, numbering 102, were continued as breeders of which three developed mammary cancer, an incidence of 2 9 per cent Cancer appeared at 633, 556, and 526 days in the three cancerous females and they gave birth to four, eight, and five litters, respectively The noncancerous $CZbF_1$ mice lived to an average age of 698 days

Muhlbock (163) sterilized females by cutting between the fallopian tubes and the uterus These agent-free females were mated with males carrying the agent, but none of the females developed mammary cancer

In another study, in collaboration with Dr M Frantz, females of the C stock were mated with males of the cancerous Z strain Fourteen animals served as controls, while 17 litter mates had their uterine horns amputated at the junction with the cervix. Ten of the operated C females, or 59 per

cent, had mammary cancer at an average age of 569 days, compared with an incidence of 50 per cent in the untreated controls which had an average cancer age of 494 days In the latter group all of the cancerous C females had cancerous CZF_1 progeny These results show that females may become infected with the MTA from males of cancerous stocks and have mammary cancer, although the females could not have any progeny

Males of the cancerous A stock have been tested for the transmission of the MTA by mating with 15 females of the C strain Five of these C females had mammary cancer at an average cancer age of 554 days, after having an average of 10 4 litters The noncancerous C females averaged 9.2 litters and lived to an average age of 599 days

Additional data were secured by mating 20 C females with males of the Andervont subline of the C3H stock maintained in this laboratory Three of these C females gave rise to mammary cancer at an average of 669 days The youngest C female with cancer was 562 days of age and ten of the *noncancerous C females survived beyond* this age None of the tumors from the C females was tested for the MTA

The F_1 progeny of this cross are being continued as breeders, but a final incidence of mammary cancer can not be given since many of this group are still living with the youngest animal being 18 months of age The data have been tabulated, but only mice have been counted where all in a litter have died These include primarily the hybrids born in the first three litters Also in other litters cancerous mice have not been included where one or more of their litter mates are living free of cancer

The number of hybrids which can be considered is 120 of which 54 or 45 per cent had mammary cancer Tumors were observed when the females averaged 595 days while the noncancerous females lived to an average of 665 days. The average number of litters born to females of the respective groups was 6.5 and 6 2

In the hybrids derived by crossing C females with males of the Andervont C3H line, only two females had mammary cancer under 400 days of age and the oldest was 762 days The incidence of 45 per cent is based upon the tabulation of all noncancerous mice which lived longer than 400 days If only those are included which survived to the average cancer age or 595 days the incidence would be increased to 54 per cent Several of the mammary tumors from F_1 hybrids have been assayed for the MTA, but the results of the tests are not yet known

These data corroborate those previously presented by Andervont and Dunn (19 22) but they are quite different from those obtained by mating males of our Z (C3H) subline and females of the C stock (table 2) Although the two sublines of the C3H stock were derived originally from the same source mammary tumors from mice of one line will not grow progressively when transplanted into animals of the other line (3)

In other investigations (68), females of the C stock were mated with Z males for three or four litters after which they were placed with Zb males without the MTA. In other instances, the C females were mated alternately with Z and Zb males In a few cases in each group the C females became infected with the agent from the Z males and the F_1 progeny born in later litters with Zb fathers continued to have a high incidence of mammary cancer In other tests young mice of the cancerous Z strain were fostered by females of the cancerous A strain and males of the group or Z mice with the A agent (Za) were tested

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with C females Mammary tumors have developed in two of the nine C females and, based upon the observation in their F_1 progeny, three of the noncancerous C females were infected

Heston and Deringer (122) made reciprocal crosses between animals of the low cancerous C57 black stock and agent-free mice of their C3H stock Incidences of seven and eight per cent were observed in the reciprocal hybrids, compared with an incidence of 38 per cent in agent-free breeding C3H females

Andervont and Dunn (22) obtained hybrids by crossing males of the dilute brown stock with C females Thirteen females were mated with males with the agent and 15 to males without the MTA The C females died without any having mammary cancer Seventeen per cent of the hybrids with agent-free fathers and 38 per cent with paternal parents of the cancerous line developed the disease The agent was recovered in one litter descended from a male with the agent

Males of another cancerous line of the dilute brown stock (D_8) have likewise been studied, again using C females Three, or 2 per cent, of their F_1 progeny have had mammary cancer but many hybrids are still under observation None of the C females became tumorous

Males of the C stock possessing the MTA may infect females of the same strain, for some C females mated to these males have died with cancer

Eleven JK females were placed in breeding pens with males of the cancerous Z stock and remained noncancerous, but two showed evidence of infection with the agent from the Z males Before infection, 15 F_1 progeny were born to these females, of which nine have died noncancerous at an average age of 182 days, and the others are living without cancer Fifteen progeny of these females were continued after they became infected, of which four are living and the other had mammary cancer at an average age of 320 days Females of the JK show a low incidence of mammary cancer when they obtained the MTA by nursing females of the cancerous Z stock (62, 68)

These data show that there is considerable difference in the sensitivity of females without the agent, of susceptible and nonsusceptible stocks, to become infected with the agent when it is transferred by males of cancerous strains, as well as variations in the ability of males of the cancerous strains to infect females, of either the same or other stocks (63)

Now that it is known that the males of cancerous stocks may transfer the MTA at the time of copulation, it is possible to explain some data obtained previously (63)

Influence of Force Breeding

During the past two decades numerous investigations have been made regarding the influence of force breeding—rapid breeding and the prevention of nursing—upon the development of mammary cancer in mice, especially in strains having low incidences These studies were undertaken primarily because Bagg and his associates (26, 29) reported that mammary cancer could be produced in females of the C57 black stock by this technique, when the young were removed as soon as they were born and the females returned to the breeding pens They reasoned that with the prevention of nursing there was retention of milk in the ducts of the mammary glands and irritating chemicals might be produced which, acting upon the epithelium, induced the development of mammary cancer

These observations could not be confirmed in the same strain by Little and Pearsons

(150) Fekete (07), and later by Bagg (27 28)

Some of the females of the C57 black stock observed by Bagg (26) in his earlier force breeding experiments had been raised by foster mothers Personal communication (50) revealed that some of these foster mothers probably transferred the agent to their fostered C57 black mice, and these were added to the group continued as force breeders. In a subsequent report Bagg (27) showed that while none of the females of one subline of this stock would develop mammary cancer when they were subjected to force breeding after they had been nursed by females of the cancerous C3H stock nine of 18 had given rise to mammary cancer and six others were living at the time Also, there was no significant difference in the incidences between those which nursed their young and those used as force breeders.

In females of the C57 black stock descended from fertilized ova which developed in the uteri of dilute brown females and which obtained the mammary tumor agent from these females of a cancerous strain the animals and their descendants were force bred part of the time (99) No variation either in the incidence or average cancer age was found between those which had from one to six litters (74 per cent at 437 days) and those having seven to 13 litters (72 per cent at 443 days)

Muhlbock (101) investigated the influence of force breeding in several groups having low or high incidences of mammary cancer In certain inbred strains or hybrids, rapid breeding appeared not only to increase the incidence but also to accelerate the development of the tumors in others, especially hybrids with a low incidence, no effect was noticed In females of the fostered line of the dilute brown stock, force breeding increased the incidence from approximately four per cent to 15 per cent provided the females had three or more litters In this stock there was considerable difference between the normal breeders and force breeders of the three sublines, and an unequal distribution of the mice, by subline could have accounted for the results

In agent-free mice of subline 2 of the dilute brown stock, Andervont and Dunn (20) found that of the animals which lived to a mean age of 20 months and had from two to five litters, less than one per cent had mammary cancer

In females of three sublines of the cancerous dilute brown stock maintained in this laboratory force breeding had no effect on either the incidence or the cancer age as compared with normal breeding (60) Considerable variation was noted in the three groups, in one force breeding delayed the average cancer age by 85 days.

At the same time (60), data were presented on the development of mammary cancer in females of the cancerous Z (C3H) stock comparing females which nursed their offspring with others used as force breeders. In the first group tumors appeared at an average age of 310 days in the force breeders and 272 days in the normal breeders the respective incidences were 80 per cent and 94 per cent

In another series, a third group of Z females was included where they were permitted to nurse their progeny for approximately twelve days before they were returned to the breeding pen The observations (60) for another group of controls or normal breeders, observed at the same time as the experimental mice were the same as for the previous study i e. an incidence of 93 per cent and a cancer age of 270 days The incidence in the second group of force breeders was 81 per cent but the cancer age was 234 days, as contrasted with 310 days in the first group The females

which nursed their young for twelve days showed the lowest incidence, or 74 per cent, and they had approximately the same average cancer age as did the normal breeders 263 days versus 270 days

Many of the females with the 12-day nursing period had engorged mammary glands resulting from the stagnation of milk. Histological examination of the mammary glands of the force breeders showed that there was little milk production, confirming the findings of Fekete (97), who stated that the functional activity of the mammary glands of mice was assured only following the stimulation afforded by suckling

Thus, any influence of force breeding upon the genesis of mammary cancer in mice could be ascribed to the influence of repeated pregnancies, and not to retention and stagnation of milk in the ducts of the mammary glands.

Other types of breeding tests have been used with regard to the genesis of mammary cancer in mice

In 1936, Fekete and Green (98) reported that complete blockage of the nipples influenced the site of tumor formation in females of a cancerous strain, but did not induce mammary tumors in females of a low cancerous stock So-called functional tests were employed by Fekete (97) in other studies In one, the females nursed for one day after which they were returned to the breeding pen, in another, the females remained with the male and many became pregnant while still nursing, in the third prolonged lactation was obtained by substituting young mice at regular intervals

Again it was reported (97) that none of these tests induced mammary cancer in mice of the C57 black stock, with a normal low incidence of mammary cancer In females of the cancerous dilute brown stock, the lowest incidence occurred in those subjected to prolonged lactation and the highest in the mice which nursed for one day Data were not given for control (normal breeding) females In reviewing these experiments in a later report, Fekete and Little (99) stated that force breeding did not increase the mammary tumor incidence of C57 black and dba mice, our data (60), mentioned above, confirmed this observation for the cancerous strain

Strong (186) obtained reciprocal hybrids by crossing animals of the cancerous C3H and low cancerous JK stocks, and the F_1 progeny were mated with the sexes kept constantly together, so that the females were in almost continuous reproductive activity, nursing one litter while the next one was developing *in utero* This method of breeding was comparable to one of the functional tests employed by Fekete (97) Strong observed that 83 per cent of the hybrids with C3H mothers and 71 per cent with JK mothers had mammary cancer, the respective average cancer ages were 425 and 476 days

A possible explanation for the high incidence in the hybrids with JK maternal parents might have been due to male transmission of the mammary cancer agent, suggested by Foulds (101), which is discussed in another section

Diet and Environmental Factors

Environmental factors, including diet, have been shown to influence the development of mammary cancer in mice

Lower incidences were observed in mice which were underfed (182), or received diets low in calories (191–193, 195 202) cystine (198–200, 203), or lysine (201) Because few of the females on a calorie restricted diet became pregnant (195), as well as from other observations (128, 158, 200, 202, 203), it has been shown that the primary effects are on the endocrine system

Even different diets each considered to be adequate may give different results in the same strain (35) and it has been found that *substitutions in* the commercial diet made during the war period were probably responsible for the altered incidence of mammary cancer found in certain groups of inbred mice (68)

Others (104 197) have determined that fewer mice gave rise to tumors when they were maintained at a temperature of 90°F than when kept between 65°–75°F In view of the results secured in the underfeeding and restriction experiments the fact that the animals housed at the high temperature consumed only half as much food and showed growth suppression may be of importance in the interpretation of these data

Andervont (9) noted that segregated females of a cancerous strain showed a higher incidence and an earlier average cancer age than did those maintained in groups of eight per pen Differences in the frequency and duration of the estrous cycles were found and it was concluded that the observations might be explained on the basis of environmental factors which exerted an influence upon the hormonal stimulation

Inherited Hormonal Mechanisms

In 1944 two independent studies (73 120) were published concerning the genetic control of an hormonal mechanism related to the development of mammary cancer in virgin females

In both experiments, reciprocal crosses were made between animals of the cancerous A and C3H stocks. In the A strain the virgin females show a low incidence of mammary cancer (38 39) whereas in the C3H strain the nonbreeders have a high incidence (2 51) In the reciprocal A × C3H hybrids it was determined that the virgin F_1 females, as well as the breeders had high incidences demonstrating that the hormonal factor which induced a high incidence in virgin females was transmitted This mechanism has been termed the mammary cancer inherited hormonal influence (55 65 71)

Studies on the hormonal mechanism in this laboratory were stimulated by the observations of Woolley et al (106 207–210) on the influence of ovariectomy on the development of mammary cancer in certain inbred strains

Although others (78 151, 165) had reported that ovariectomy would reduce the incidence of mammary cancer in mice and that the younger the animals were at the time of operation the lower the incidence would be Woolley and his associates found that when *day-old mice of certain stocks* were operated the incidence of mammary cancer did not differ significantly from the virgin controls In the ovariectomized females of strains which developed mammary cancer adrenal cortical nodular hyperplasia was noted These females showed a cornified smear and it was concluded that the altered adrenals had simulated the function of the ovaries

Because the ovariectomized females of two cancerous strains which showed adrenal cortical hyperplasia also developed mammary cancer as virgins (100, 207–209) while gonadectomized females of another which had a low incidence as virgins remained in the *castrate state with no evi*dence of hormonal stimulation of the secondary sex organs (81) it was decided to investigate the hormonal pattern of postcastrational adrenal alteration and its possible relationship to the development of mammary cancer especially in virgin females

The initial observations made on ovariectomized females of the C3H (208) and the

A (81) strains were confirmed (183–185) and it was determined that the tendency to develop postcastrational adrenal alterations was transmitted. Also, in these two strains and their hybrids, high incidences of mammary cancer were seen in the ovariectomized females of the groups which also had high incidences as virgins (71, 73), or which had the mammary cancer inherited hormonal influence

Other inbred strains have been tested for the transmission of the mammary cancer inherited hormonal influence by crossing females of the A strain with males of the stocks being investigated Several have been found to carry this hormonal pattern, they include, in addition to the Z or C3H, the C, D_2, D_8, I, (60, 65, 72, 131) and probably the CBA strain (68), all these stocks show postcastrational adrenal hyperplasia Breeding females of the I stock remained relatively free of mammary cancer (2, 6, 65) when they possessed the mammary tumor agent, however after males of the I stock were mated with females of the A stock, where the virgin incidence was four per cent, 72 per cent of the AIF_1 virgin progeny had mammary cancer (65).

Some data are available on the possible physiological effect of the inherited hormonal influence Deringer, Heston, and Andervont (79) determined that in the groups with the higher tumor incidences, the vagina of the females opened at an earlier age

In other studies, ovaries or adrenals have been transplanted into either ovariectomized or adrenalectomized-ovariectomized animals Under these conditions, the grafts perhaps from donors of different inbred stocks transplanted in F_1 hybrids, would be subjected to a comparable pituitary stimulation, and the hormones would act upon, and be metabolized by, genetically identical tissues Significant differences in the observations, especially as they influenced the development of mammary cancer, may be assumed to be at least partially due to hormonal effects associated with inherited hormonal patterns (72, 131–133)

Following the grafting of ovaries into ovariectomized animals of the same stock or F_1 group, the incidences and average ages for mammary cancer were found to be similar to those seen in virgin females of the respective groups (72, 131) However, when ovaries from the A strain, with a low incidence of mammary cancer in virgins (71), were grafted into gonadectomized F_1 ($A \times Z$) females, the incidence of mammary cancer (57 per cent) was nearly as high as when ovarian grafts from donors of the Z stock were tested (66 per cent) (72, 131) A difference in the inherited hormonal function of the ovarian tissues was indicated because the tumors appeared approximately 100 days earlier in the F_1 females bearing Z-strain ovaries than when A ovaries were grafted In the intact animals of the parental Z and A stocks, a variation in the pituitary gonadotropic stimulation was probably responsible for the morphological difference seen in the ovaries, but this was not evident in the grafted ovaries after a period of three months

The transmission of the postcastrational adrenal lesions, observed by many investigators, may be summarized thus (132 133): "The tendency for adrenals to become carcinomatous was dominant over that for hyperplasia to develop, but that both of these were dominant over the tendency for no marked alteration to appear."

Other studies (132) on gonadectomized animals observed in our colony, where seven inbred strains and eight hybrid crosses have been tested, show that although there was considerable variation in the response in the various strains of mice, the animals

of a given inbred stock, or their F_1 hybrids, responded in a very constant manner These data included the time required for the appearance of a partially cornified smear the histology of the adrenal alterations etc

When adrenals were grafted into adrenalectomized-gonadectomized animals the characteristic postcastrational adrenal changes were reproduced quite well in the grafts, demonstrating that the variations noted in the changes in the adrenals of different inbred stocks of mice after ovariectomy were probably due to inherited differences in the responsiveness of the adrenal tissue itself

Following the observations of hybrids of various generations it was suggested that the same genes do not control the inherited susceptibility and the inherited hormonal influence for mammary cancer although genes common to both factors might exist (71) Also (65) when two stocks possess the inherited hormonal influence the same genic make up may not be involved in those strains.

Other inbred strains although they develop postcastrational adrenal changes, transmit inherited hormonal patterns that do not induce the high incidence of mammary cancer characteristic of the action of the inherited hormonal influence or in excess of 60 per cent in females maintained as virgins

Gonadectomized mice of the CE stock develop adrenal cortical carcinoma (212–217) which is transmitted (60 204) While the mice of the CE stock have been found to be susceptible to the development of mammary cancer (60 62 70) a high incidence has not been noted in virgin females of the CE strain with the agent or in $ACEF_1$ (A♀ × CE♂) hybrids (60 68) However when CE females with the MTA were mated with males transmitting the mammary cancer inherited hormonal influence such as the susceptible Z or nonsusceptible I strains nearly all of their female F_1 progeny, kept as virgins have developed mammary cancer (62 68 70) In the CE♀ × I♂ cross, after the CE females obtained the MTA by nursing females of the Z stock in litters where all the F_1 hybrids are dead, 25 virgins and 24 breeders, or 100 per cent in each group had mammary cancer The respective average cancer ages were 313 and 246 days Fifty three other virgin females are members of litters where one or more are still living and of these 31 have had mammary cancer and one died nontumorous

Another inherited hormonal mechanism has been described which appears to either inhibit the development of mammary cancer or delay the time of appearance not only in virgin females but in breeders as well (62 67 72) This is transmitted by mice of the NH stock where spontaneous adrenal tumors may develop in animals over one year of age due to physiological castration, however the adrenal lesions may be accelerated by ovariectomy (102 103 108, 138 141)

The inherited hormonal influence which induces mammary cancer in virgin females, is dominant over the hormonal pattern of the NH stock (the incidence in $ZNHF_1$ virgins was 94 per cent) although some influence of the latter may be seen in determining the average cancer age In the $ANHF_1$ virgins and breeders the respective incidences were 16 per cent and 43 per cent but when the $ANHF_1$ females were mated with Zb males the incidence in their progeny, maintained as virgins was 61 per cent

The incidence of mammary cancer in $ANHF_1$ breeding females or in animals having the MTA the inherited susceptibility and the hormonal stimulation of breeding was only a little higher (43 per cent) than the incidence in agent-free C3H breeding females (38 per cent) (122)

These data indicate that, based upon the postcastrational adrenal alterations, several different physiological hormonal mechanisms may be demonstrated in regard to the development of spontaneous mammary cancer in mice Further experimentation is needed to determine the effects of each mechanism, the hormonal production of the adrenals under various conditions, etc

Following the development of adrenal cortical hyperplasia or carcinoma, it has been reported (81, 204, 205) that pituitary tumors also would develop in gonadectomized animals of certain inbred stocks, such as the dilute brown, C3H, CE, and their hybrids It was postulated that the development of mammary cancer in these gonadectomized males and females was dependent, in addition to the genetic susceptibility and the mammary tumor agent, upon the hormonal influences supplied by the altered adrenals and hypophyses Mammary cancer appeared in a limited number of animals

It has yet to be reported in the literature that gonadectomized animals of any stock will give rise to mammary cancer if the virgin females of the strain do not show a high incidence The high incidence in virgins was shown to result, in part, from an inherited hormonal mechanism (73, 120) Whereas ovariectomized females of certain stocks which possessed this hormonal mechanism had incidences of mammary cancer similar to virgin females (72, 100, 131, 132, 183–185, 207–209), in gonadectomized males of the dilute brown stock either low incidences (165, 209) were observed or mammary tumors did not develop (132) This would show a sex difference in certain strains in regard to the genesis of mammary cancer following gonadectomy

The importance of the observations made by Dickie, Woolley, and Little (80, 81, 204–206) may be that some strains will develop pituitary abnormalities in addition to postcastrational adrenal cortical alterations Whereas mice of the C3H and dilute brown stocks (60, 72, 73, 120, 183–185) transmit the mammary cancer inherited hormonal influence, the hormonal pattern transmitted by mice of the CE stock did not induce the expected incidence in virgin females, of the inbred strain or the $ACEF_1$ generation, yet they are susceptible to the development of spontaneous mammary cancer (60, 70, 72).

The importance of the role of the adrenals in the genesis of mammary cancer in mice has been demonstrated by the work of Shimkin and Wyman (181) Using a strain where the incidence in virgin females was found to be 85 per cent, only nine per cent of the adrenalectomized-ovariectomized females bearing pellets of desoxycorticosterone acetate died with mammary cancer

Induced Mammary Cancer

Lacassagne (146–148) was the first to demonstrate that mammary cancer could be induced in mice following the injection of hormones Later work showed that such tumors could be produced in mice of high cancerous strains (5, 43, 45, 105, 107, 108, 178, 180), whereas mice of strains without the MTA developed few, if any, mammary tumors Hormone-induced mammary tumors were not produced in control animals of the low cancerous C57 black stock (190), but after they had been fostered by females of a cancerous strain, the incidence in treated males was 33 per cent (194)

Tumors of the mammary glands, together with granulosa-cell tumors of the ovaries, may be produced following gamma irradiation (153) in agent-free females of the C3H stock

Subsequent to the observations of Maisin and Coolin (154) that carcinogenic hydrocarbons would accelerate the development of mammary cancer in mice, numerous investigators have confirmed their work and extended our knowledge of this interesting

and important aspect of the cancer problem This consideration will of necessity be limited and various factors, such as subline differences within inbred stocks dosage, method of application of the agent, which may influence the carcinogenic induction of tumors in some studies but not others will not be discussed References to these problems will be found in the citations given here

That the time of appearance of mammary cancer in mice could be expedited was established in many laboratories (75 76 95 96, 140 142 143 157 159) also that tumors could be induced in mice with a low incidence of spontaneous mammary cancer considered to be nonsusceptible (75 76 90, 187 189) In females of the same susceptible stock, with and without the MTA, mammary tumors were induced earlier and in a higher incidence in the mice which possessed the agent (20 140) and the tumors appeared earlier in breeders than in non breeders (142) although in agent-free mice, the addition of cholesterol-stilbestrol pellets did not increase the incidence compared with the hydrocarbon alone (20)

Following the application of methyl cholanthrene Dmochowski and Orr (90) were able to induce mammary tumors in breeders and virgin females of the low cancerous C57 black and cancerous C3H stock but not in the males yet the combined action of the hydrocarbon and estrone produced tumors in males of both stocks The mammary tumors from the males of the C57 black stock were found to be free of the agent but the MTA could be recovered from the tumors of the C3H males (91) Tumors induced in susceptible but agent-free mice do not possess the agent (20 74)

Histology

Dunn (20) has stated that while it would be most difficult to make a rigid classification of the histopathology of mammary tumors in mice an attempt should be made to determine the possible types of morphologic variation encountered in the tumors of mice of different inbred strains, and in various experiments However, Dunn cautions that every tumor would not fit into an exact category and that different individuals probably would not arrive at the same classification for every tumor, especially if they might be looking at different sections

The following groups have been listed by Dunn (93 94) with their synonyms

Adenocarcinoma, Type A (Typical mammary tumor mammary adenocarcinoma alveolar carcinoma) In these tumors there is predominance of the acinar structure

Adenocarcinoma Type B (Papillary cyst adenocarcinoma intracanalicular adenocarcinoma carcinoma simplex) There is no definite demarcation between tumors of Type A and B differentiation is based primarily upon the amount of acinar structure

Adenocarcinoma, Type C (Fibroadenoma, adenofibroma) These tumors are made up of many epithelial lined cysts, with the lining closely invested by a layer of spindle cells

Adenoacanthoma (Keratinized mammary tumors adenosquamous carcinoma adenocancroid mammary tumor with squamous metaplasia)

Carcinosarcoma (Carcinoma with spindle cell formation, anaplastic carcinoma, mixed tumors)

Sarcoma of the mammary gland area (Mammary sarcoma.)

Miscellaneous types consisting of bizarre tumors

Transition stages between the carcinosarcoma and sarcoma may be found The probable origin, according to Dunn is from the mammary connective tissue with the interlacing bundles enveloping the mammary ducts

A purely squamous mammary carcinoma has been described by Pullinger (177) but

Dunn (20) stated that they either have not seen this type or they have failed to recognize it

A few mammary tumors may appear in old females of susceptible strains when they do not possess the mammary tumor agent, and Gardner (107) has found that they grow slowly and many are of the squamous cell type

Following the examination of spontaneous mammary tumors from cancerous strains, Dunn (94) observed that less than one per cent could not be classified as adenocarcinoma, Type A or B, however, of the mammary tumors which developed in agent-free C3H females, 23 of 60 were not of the types usually seen in mice which possessed the MTA

Muhlbock et al (164) were of the opinion that the structure of the tumors which appeared in breeding females of the fostered dilute brown stock did not indicate the presence or absence of the agent However, they reported a greater variety of histologic pictures and a lower percentage of tumors with acinar solid structure, and related varieties, as compared with mice with the agent

Andervont and Dunn (20) did not find mammary tumors in mice of their dilute brown stock without the MTA, but observed five histologic types induced by the action of methylcholanthrene alone or in conjunction with hormonal stimulation (stilbestrol-cholesterol pellets), all types arose in mice of the same age However, the pellets did not enhance the effect of the hydrocarbon alone Of the 20 tumors induced by methylcholanthrene alone, eight were diagnosed as adenocanthomas, three as carcinosarcomas, and two as belonging to the miscellaneous type Eighteen tumors were produced by the combined action of the hydrocarbon and hormone pellets and, of these, nine were adenoacanthomas and four carcinosarcomas When mammary tumors were induced in mice which possessed the MTA, 27 of 29 tumors were of the type usually found in mice with the agent

The authors (20) concluded that while some of the carcinogen-induced tumors were indistinguishable from those in which the agent was involved, the results indicated that the histologic structure of the tumors was dependent upon their etiology Dmochowski (87), concluded from the study of tumors which appeared in hybrid mice that the frequency of occurrence of various types of mammary tumors, and the age at which they developed, appeared to be influenced by the genetic constitution of the animals, with the squamous type tumors developing in older mice

Many workers have noted squamous metaplasia to occur in mammary tumors induced by carcinogenic hydrocarbons (20) Of the 45 tumors from NH mice, Strong and Williams (189) *found that eleven were* of the squamous metaplasia type with keratinization, and five were of the "scirrhous" type

By the percutaneous application of methylcholanthrene to mice of the same stocks and their hybrids with and without the mammary tumor agent, Kirschbaum et al (139, 143) found that susceptibility to the induction of mammary cancer was not common to all inbred strains, and that it was not correlated with the susceptibility to spontaneous mammary cancer Tumors appeared earlier, and usually in a higher incidence, in mice of the same stock with the MTA, but histologic evidence for the carcinogenic induction of these tumors could be seen, especially in the proliferative epithelial response Thus, the evidence did not favor the concept that carcinogens accelerated the sequence of alterations seen in the histogenesis of spontaneous agent tumors in mice

Summary

The experimental use of inbred strains and their hybrids has made it possible to demonstrate several causative factors in the etiology of spontaneous mammary cancer in mice, which usually develop due to the *interaction of* 1) *an inherited susceptibility* 2) hormonal stimulation and 3) the mammary tumor agent (MTA) The agent has the properties of an infectious agent or virus and is transferred from mother to offspring in the milk A high incidence of mammary cancer in virgin females may be correlated with an inherited hormonal pattern or mechanism called the mammary cancer inherited hormonal influence Breeding will overcome the lack of this inherited hormonal influence in most groups, and accelerate the disease in those which have the hormonal factor

No evidence has been found to suggest any nursing influence for the genesis of breast cancer in humans In several surveys, data were analyzed only from the standpoint of breast versus bottle feeding and where all malignancies of the breasts in humans were assumed to have the same etiological causative factors

Many of the observations obtained in mice where identical animals may be used as controls and the experimental conditions kept constant could not be interpreted upon these simple criteria for in mice

1 In addition to the milk, the MTA may be transferred by the injection or feeding of extracts of tissues, including blood, from infected animals.

2 It may be transferred by males of cancerous strains at the time of coitus to infect females of either susceptible or resistant stocks

3 After agent-free females of one susceptible stock were mated with males of a high cancerous strain, 58 per cent of the females developed mammary cancer because of transmission and infection with the agent from the males

4 Females of the same stock, which were unable to have offspring because of the amputation of the uterine horns showed an incidence of 59 per cent when they were housed with males of the same cancerous strain

5 The agent may appear in females of susceptible or resistant stocks which had neither been fostered by animals of cancerous strains nor injected with extracts containing the agent.

6 As soon as females become infected with the MTA from any source, they will transfer the agent in the milk to their progeny, although the mothers may not give rise to mammary cancer

7 The agent may be transferred for at least ten generations in a strain where the breeding females have a low incidence of spontaneous mammary cancer

8 The first generation progeny, produced by mating animals of high cancerous strains, may or may not have similar incidences of mammary cancer and average cancer ages This indicates a difference in the tumor inducing activity of the agents from these inbred strains in mice (F_1 hybrids) having the same genetic constitutions

9 The development of mammary cancer in mice may be influenced by diet, temperature and other environmental factors

10 If force breeding (rapid breeding with the prevention of nursing) exerts any influence upon the genesis of mammary cancer in mice it would result from the increased hormonal stimulation of repeated pregnancies and not from retention and stagnation of milk

11 The activity of the MTA in breeding females of a susceptible stock may be partially suppressed by an inhibitory inherited hormonal pattern

12 The physiological effects of another

inherited hormonal pattern, the mammary cancer inherited hormonal influence, is dominant over the inhibitory mechanism, and will produce a high incidence in virgin females which have the MTA and the inherited susceptibility

13 The presence of the MTA is not necessary for the development of mammary cancer in mice, as incidences of approximately 40 per cent to 50 per cent have been observed in agent-free females of some inbred strains and hybrid generations

14 Carcinogenic hydrocarbons will induce mammary cancer in agent-free animals of strains which are either susceptible or resistant to the development of spontaneous mammary cancer

15 The histologic structure of mammary cancers from mice of high cancerous stocks and agent-free animals may be indistinguishable, but greater variation has been described in the spontaneous and induced tumors of agent-free mice which may be correlated with their etiology

The actual role of the mammary tumor agent, with the properties of an infectious agent or virus, is not known in the genesis of mammary cancer in mice With few exceptions, females which lack the agent will have a low incidence, and it usually requires, on an average, over twice as long for the agent-free mice to develop their tumors

It has been suggested (118, 119) that the MTA should be classified with the nongenetic causative factors, since the absence of the agent does not prevent the development of mammary cancer in certain animals but its presence increases the probability that the disease will occur Or, while mice may have mammary cancer without the MTA, or virus, one must obtain the virus of other diseases, such as small pox, to contract those diseases

These representative observations obtained by the use of experimental animals would indicate that if an agent might be present, and it had similar characteristics and properties as the MTA in the genesis of mammary cancer in mice, it is doubtful if data could be secured to demonstrate such an agent as a causative factor in the development of one or more types of breast cancer in humans

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CHAPTER V

The Pathology of Cancer of the Breast

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The mature human female mammary gland consists of 15 to 20 lobes each composed of a single nipple duct with its ampulla just beneath the areola, and its many tributary ducts draining the corresponding lobules The mammary lobules are clusters of small blind ducts set off from the surrounding tissues by a characteristic stroma This loose-textured cellular intralobular connective tissue is in sharp contrast with the interlobular connective tissue which is of more usual character

The mammary ducts are lined by two layers of cells the basal layer being more or less flattened against the basement membrane whereas the cells of the superficial layer are oriented perpendicularly to the basement membrane becoming progressively taller as the ducts become larger

The mammary gland is not a static organ but continually changes under the influence of altered hormonal environment (see Chapter III) Some proliferative activity and often secretion are evident immediately after birth as the result of the same stimuli responsible for the mother's lactation These changes regress within a few weeks, and the breast remains inactive until the onset of the endocrine changes of adolescence At this time the mammary ducts elongate and branch and there is an increase of the fibrous stroma with accumulation of fat Finally the mammary lobules develop

During the years of cyclic ovarian function the mammary lobules undergo periodic change with the menstrual cycle The lobules tend to enlarge with the onset of the corpus luteum phase of the cycle The specialized intralobular connective tissue becomes looser and both the connective tissue and epithelial cells are larger The lumina of the ductules open and contain secretion These changes are progressive although variable from one breast to another as well as from one lobule to another within the same breast They reach their maximum at about the onset of menstruation The regressive changes that follow involve closing of the tubules and shrinking of their component cells and condensation of the stroma with infiltration by lymphocytes (14 18)

Pregnancy of course results in a more profound alteration of the mammary gland The earliest changes are similar to those of the premenstrual period but there is further proliferation of the ducts and in the second trimester large lobules composed of secretory acini develop The intralobular connective tissue is scanty In the final trimester the changes are predominantly those of secretion as opposed to proliferation although the status of full secretory activity is not attained until three or four days after parturition Involution follows the cessation of lactation rather promptly although isolated lobules may on occasion

continue to secrete for periods as long as many years

With increasing age and the approach of the menopause the intralobular connective tissue becomes more compact, richer in collagen fibers and poorer in cells There is an increase of elastic tissue, especially just outside the loose connective tissue about the large and medium-sized ducts The amount of collagen in the interlobular connective tissue and the amount of fat often increase After the menopause atrophy of the epithelial elements is accelerated and during the next few years, the lobules gradually disappear (23) The age at which this process begins and its rapidity and completeness are subject to great individual variation

Etiology and Pathogenesis

The human mammary gland is subject to many diseases, of which cancer is by far the most important, although not the most frequent Breast cancer is primarily a disease of the female, but it should be noted that it does occur in the male (see Chapter XX)—approximately one case being seen for every 100 encountered in the female (1, 48) Since the pathology of the disease in the male is not essentially different from that in the female, it will not be separately considered further (42, 45)

The exact cause of human mammary cancer is not known No doubt many factors are concerned but for the most part precise data are wanting for establishing the nature of the relationship of such factors to malignant tumors A great deal of information has been obtained from experimental observations on mice, a species in which spontaneous breast cancer is common It has been shown that there are three major factors concerned in the genesis of spontaneous mammary cancer in mice They are inherited susceptibility, hormonal stimulation and the so-called "mammary tumor agent" (7) (see Chapter IV) The relationship of similar factors to human mammary cancer has been the subject of much study and speculation

Whereas the influence of heredity upon the spontaneous development of mammary carcinoma in mice is reasonably well understood, varying among different inbred strains, the evidence for the role of heredity in the etiology of human breast cancer is conflicting It has been implicated in large part because of the observation of occasional families with an overwhelming familial history of the disease Most of the studies designed to clarify this point reach the conclusion that there is an hereditary factor in the etiology of breast cancer, and it is even suggested that when the daughters of women with breast cancer develop breast cancer themselves, they do so at an average age ten years younger than their mothers (35) Murphy (38), however, finds no greater incidence of breast cancer in the female relatives of breast cancer patients than in the relatives of controls (See Chapter VIII)

There exist many facts to document a relationship between mammary cancer and hormonal environment in addition to the obvious one that the disease is almost exclusively one of the female Castration, especially at a young age, lowers the incidence of breast cancer in mice (25, 31), and there are data suggesting that the disease is relatively uncommon in the human castrate as well (21) Also, it is doubtful if an authenticated instance is on record of breast cancer occurring in the human pre-pubertal female Conversely, the stimulating effect of estrogenic substances on breast cancer in young women is well known, and Huseby and Thomas (23) have described the proliferative activity induced in normal breast tissue of postmenopausal patients by the administration of estrogens Paradoxically, however, cancers were frequently regressing at the

same time that uninvolved elements of the same breast were proliferating Available evidence indicates that breast cancer is relatively more common in single than in married women, in women without children and in mothers with a history of abnormal lactation Lewison and Allen (28) suggest that the common denominator may be the failure of physiologic function (see Chapter VIII) Geschickter (18) has presented data indicating that a late menopause was more frequent in women with breast cancer than in those without the condition

Estrogenic substances have been demonstrated to produce breast cancer in male mice of suitable strains (24) and it has been suggested that estrogen administration may be causally related to human mammary carcinoma (4) However actual proof is lacking and the paucity of reports of suspected cases in contrast with the wide extent to which estrogenic substances are utilized clinically suggests that exogenous estrogen is probably not a significant factor

The problem of the relationship of *benign mammary disease* to cancer is closely related to that of hormonal environment and has been intensively investigated (see Chapter VI) Certain benign conditions, notably fibroadenomas (except in the rare circumstance of development of malignant cystosarcoma phyllodes) and inflammatory lesions almost certainly are not to be considered as predisposing to cancer Argument centers chiefly about *chronic cystic mastitis* The incidence of co-existent carcinoma and chronic cystic mastitis is difficult to appraise accurately since the criteria that have been used for the diagnosis of chronic cystic mastitis are so variable Data for the incidence of chronic cystic mastitis in the population at large suffer from the same difficulty

From a statistical and follow up study of two large series of cases Warren (46) has derived data indicating a higher incidence of carcinoma in women who have had previous operations for 'chronic mastitis and related conditions," particularly in women between the ages of 30 and 40 He calculated a breast cancer attack rate for women in this age group with such history 11 7 times that for the general female population of Massachusetts in the same age range For women over 50 the corresponding ratio was 2.5 times and for the whole group 4.5 times The study assumes that "a large proportion of women with chronic cystic mastitis are operated upon

Foote and Stewart (14) have demonstrated transitions from orderly and disorderly or atypical hyperplasias or papillomatosis to intraductal and finally invasive carcinoma However such transitions can not be demonstrated in a majority of cases and they believe that cancer can arise in a previously normal breast as well as in a previously diseased one

Frantz and her collaborators (17) in the most extensive necropsy study thus far published, using carefully defined diagnostic criteria find an incidence of chronic cystic mastitis in so-called ' normal breasts of 53 per cent—a distinctly and probably significantly lower incidence than in breasts removed for cancer (79 per cent)

At the present time it seems reasonably well established on statistical as well as morphologic grounds that breast cancer occurs more often in the breast which has been the site of chronic cystic mastitis than in the previously normal breast and that cancer at times takes its origin in the proliferative changes so frequently associated with chronic cystic mastitis (29) However the precise frequency with which cancer arises on such a background is unknown and criteria are wanting to define which benign breast lesions have a special predisposition to malignant change

In 1936 Bittner (6) demonstrated that an agent that was transferred in the milk from mother to offspring was an important factor in the etiology of mammary cancer in mice (see Chapter IV) This demonstration was accomplished by foster-nursing experiments wherein mice newly born of a low cancer strain mother, if suckled immediately after birth by a mother of cancerous stock, eventually developed an incidence of breast cancer approaching that of the foster-mother's strain This factor or agent, transferred from mother to young shortly after birth and producing mammary cancer much later in the life of the animal, has the characteristics of a filtrable virus The agent may be extracted from most of the tissues of the animals carrying it and can be transferred by injection as well as by feeding and also by the male at coitus (8) It remains active after lyophilization, filtration, desiccation and treatment with glycerin but loses its activity when heated to 56°C for a half hour (7)

This work, relating mammary carcinoma of mice to a virus or virus-like agent, has stimulated efforts to demonstrate a similar factor in humans To date there is no evidence that a nursing influence plays any part in the human disease, but the problem is infinitely more complex in humans because of their much longer life span and because many variables, including the all-important one of genetic make-up, cannot be controlled

Mammary cancer has been produced in mice by chemical carcinogens (9), other factors, such as diet, may also have some etiologic significance No carcinogenic substance has been incriminated in the causation of human mammary carcinoma, although, as noted above, the role of estrogens has been the subject of speculation

Although the importance of roentgen rays in the production of some forms of cancer, notably of the skin, is well known, only a single case of breast cancer has been recorded wherein an etiologic role has been suggested for them (30) This was a case of widespread multicentric mammary carcinoma first recognized ten years after protracted radiation therapy for Hodgkin's disease protruding through the chest wall underlying the breast

It is clear that the patient who has had a cancer of one breast has a significantly greater chance of developing cancer of the remaining breast than has her sister of the same age without such history (14) Among 724 breast cancer patients, Fitts (12) found 66 instances of bilateral disease—an incidence of nine per cent Twelve of these patients had been treated for breast carcinoma previously and came under observation when they developed the second tumor Thirteen (1 8 per cent) presented with simultaneous bilateral carcinomas, and 41 (5 9 per cent) developed their second cancer while under observation following treatment of the first—usually within three years Some of these patients have been followed for as short a time as one year, the maximum follow-up was ten years It is impossible to be certain how many of these cases represent spread from the other breast and how many are independent primary tumors

Classification

Many of the variations in the morphology of mammary gland cancer have no known bearing upon clinical behavior, degree of malignancy or prognosis The many classifications based on such variations are of little practical value Those classifications of mammary cancer which do have a relationship to prognosis suffer from the common defect that a majority of the tumors fall into a morphologically indeterminate group. A classification (15, 42) we have found useful follows

I *Carcinoma*

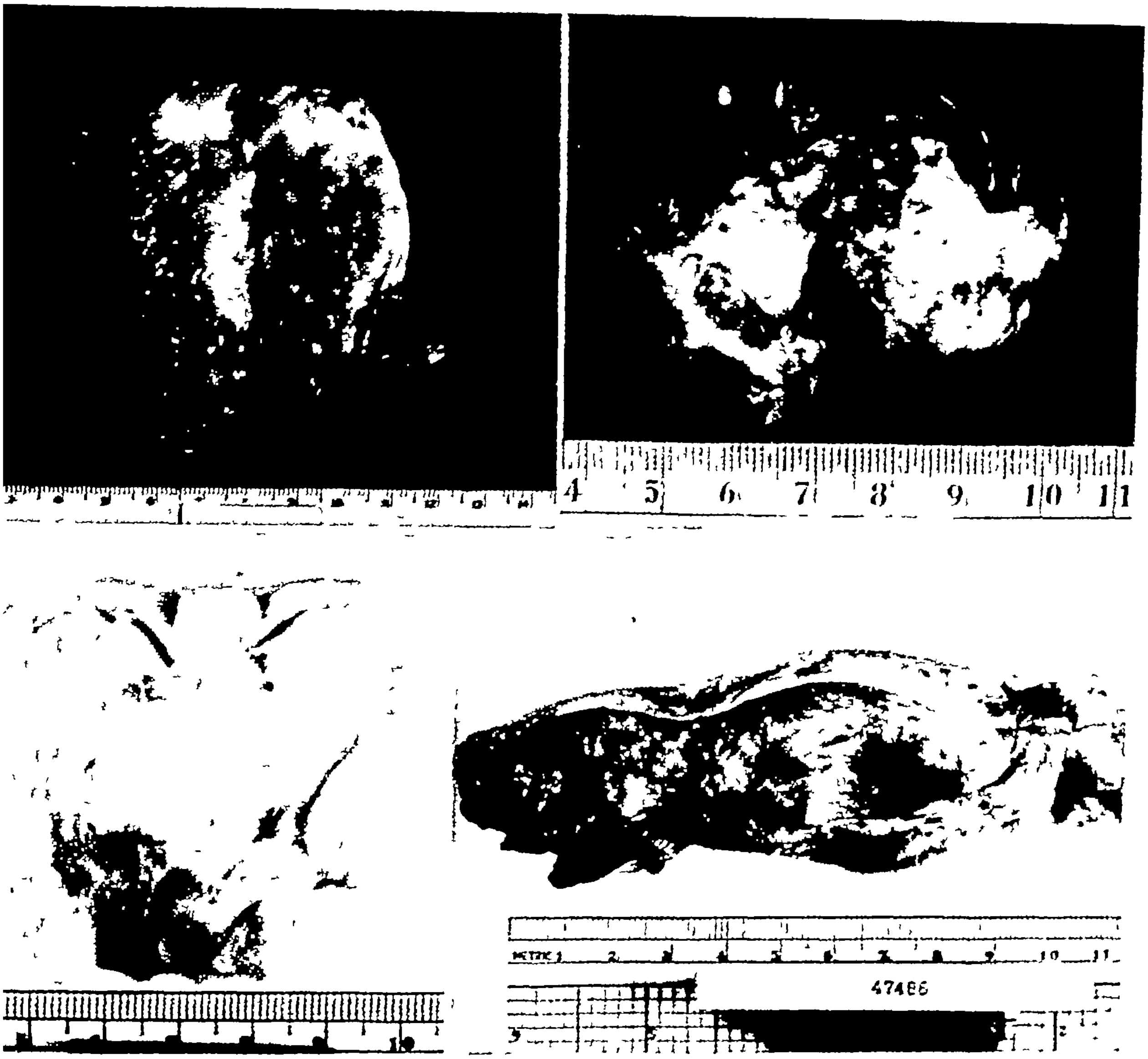

PLATE I

Upper left, intraductal carcinoma of the breast The tumor-distended ducts appear as yellow or grey-white nodules

Upper right, colloid carcinoma The glairy character of the cut surface of the tumor is apparent

Lower, two carcinomas of no special type The tumor on the left tends toward circumscription The commonly observed "chalk-streaks" are evident The tumor on the right, although small illustrates the manner in which mammary carcinoma invades the surrounding tissues and causes fixation of the skin and pectoral fascia

- A. Intraductal (6 per cent)
- B Infiltrating
  1. Papillary carcinoma (4 per cent)
  2. Colloid carcinoma (4 per cent)
  3. Medullary carcinoma with lymphoid infiltration (4 per cent)
  4. Carcinoma of no special type (70–77 per cent)
- C Relatively rare carcinomas (2 per cent)
  1. Apocrine carcinoma
  2. Squamous cell carcinoma
  3. Adenoid cystic carcinoma
  4. Carcinoma with pseudosarcomatous metaplasia
- D Paget's disease of the nipple
- E Inflammatory carcinoma (3–4 per cent)

II Sarcoma
- A Malignant cystosarcoma phyllodes
- B Miscellaneous sarcomas

I Carcinoma

A Intraductal Carcinoma

Mammary carcinoma confined to the duct system offers the patient approximately twice the chance of five year survival of the average carcinoma. That the survival rate does not approach 100 per cent is accounted for by the observation repeatedly made in this laboratory and elsewhere that even very careful pathologic examination so long as it does not include serial sections does not afford complete assurance that tumor cells have not escaped from the ducts and invaded the mammary gland stroma or lymphatic vessels. Approximately 6 per cent of mammary carcinomas may be classified as intraductal on the basis of reasonably thorough (but routine rather than exhaustive) pathologic study Grossly, intraductal carcinoma may be evident only as dilated ducts which may be widely distributed throughout the breast but are more often limited to one mammary segment The ducts may contain friable grey or white tissue or if the tumor is of the so-called comedo variety, cores of yellow, paste like detritus which may be expressed from the ducts on pressure, thus simulating a comedone (Plate IA)

Microscopically, the intraductal carcinomas show a wide variety of morphologic growth patterns We have not subclassified them because many of these morphologic variations may be seen within a single tumor (figs 37, 45B and C) At times the distinction between benign intraductal papillomatosis and intraductal carcinoma is not clear-cut the difference being one essentially of degree of cell atypism In general the malignant lesions show little stroma or vascularization progressing from branching stalks extending into the duct lumen through a stage where projecting processes of tumor cells anastomose to bridge the duct and produce multiple lumina to more or less solid packing of the duct with cancer cells The latter situation obtains in the so-called comedo carcinoma where cellular atypism is marked and central necrosis often a striking feature (fig 45B) Infrequently intraductal carcinomas may be associated with the production of abundant mucin (fig 37A) The uncommon intraductal carcinomas that tend to maintain a papillary pattern throughout may present a particularly difficult problem in differentiation from benign papillomatosis A few intraductal carcinomas are confined to the terminal ramifications of the mammary ducts This variant the lobular carcinoma in situ" of Foote and Stewart (13) often goes unrecognized Although the involved lobules may be visible grossly they are not obviously abnormal. Histologic recognition of this tumor form is almost equally difficult The cells are somewhat enlarged and usually lack cohesion but atypism is not striking They form dis-

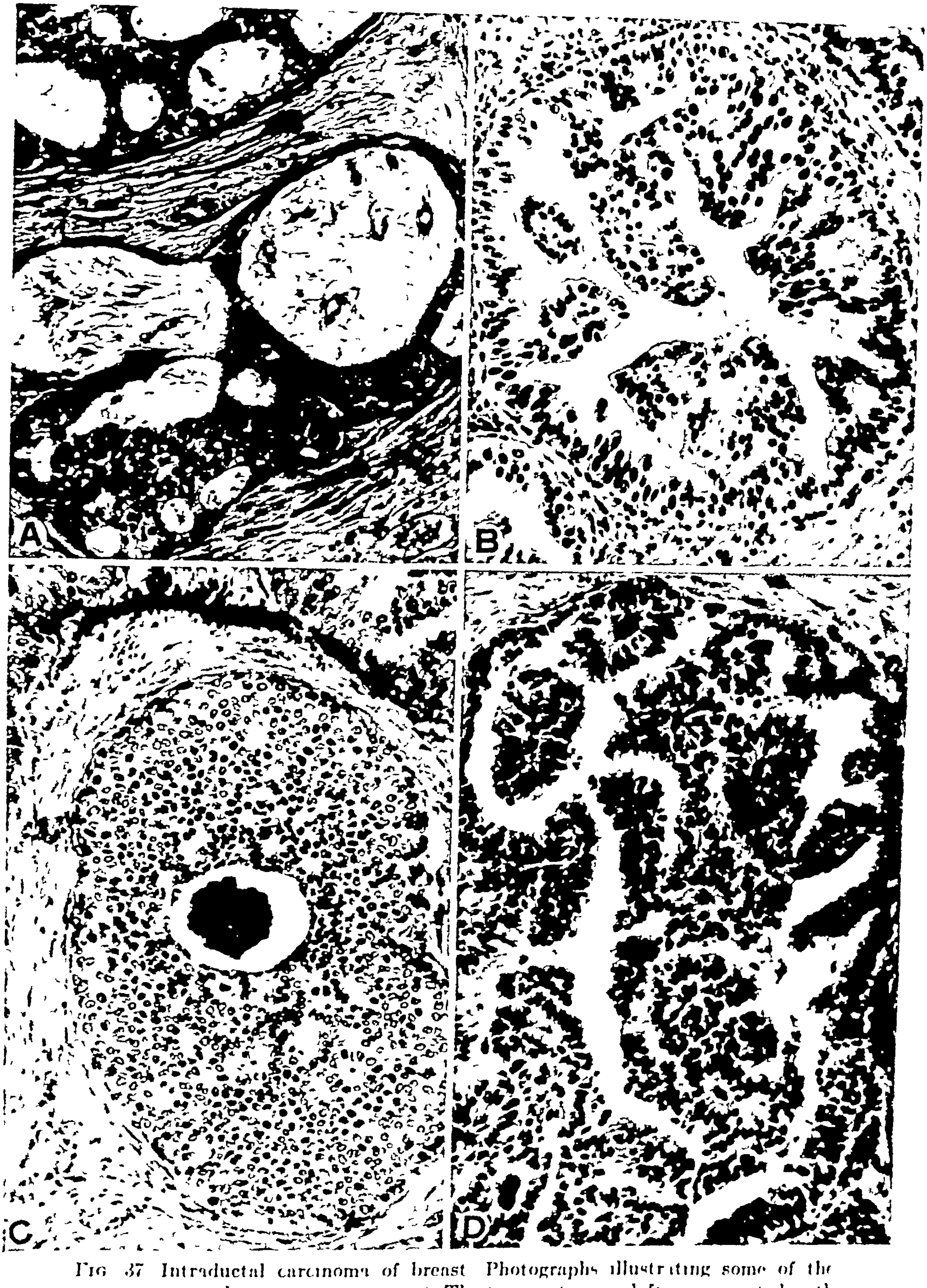

Fig. 37 Intraductal carcinoma of breast. Photographs illustrating some of the varying patterns this tumor may present. The tumor at upper left is associated with abundant mucin production. The other three photomicrographs are all from one tumor (×165). C and D are reproduced from "The significance of nipple discharge" by Fitts, Maxwell and Horn, Annals of Surgery, Vol. 134, pp. 29-39, 1951, with the permission of J. B. Lippincott Co., publishers.

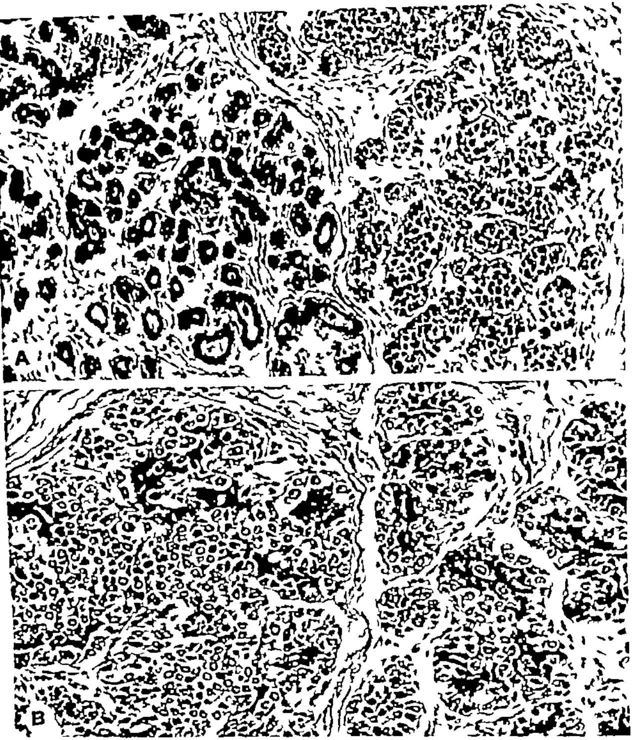

FIG 38 Lobular carcinoma in situ Above a cancerous lobule is in contrast with an essentially normal lobule at left (×105) Below higher magnification illustrating a greater degree of cellular atypism than is usually seen in this type of tumor (×250)

orderly groups filling the ducts and obliterating the lumina (fig 38)

B Infiltrating Carcinoma

1 **Papillary carcinoma** is a slow growing tumor which tends to metastasize late In the material studied at the hospital of the University of Pennsylvania the five year survival rate is 50 per cent better than that for the average mammary carcinoma Roughly 4 per cent of mammary carcinomas fall in this category Grossly the papillary

FIG 39 Papillary carcinoma of female breast (×195)

carcinomas tend to be circumscribed and they may attain large size The abundant stroma that characterizes so many breast cancers and is responsible for the diagnostic fixation signs, is inconspicuous in the tumors of this group, which tend to be soft and friable Necrosis is common and may involve a major portion of the tumor, greatly complicating the problem of diagnosis Microscopically, the basic pattern is that of branching papillae of varying complexity The papillary structure may be obscured by interanastomosis of the fronds Atypical cellular features are often not marked, although a tendency to multiple layering of the cells, nuclear pleomorphism and hyperchromatism, loss of uniform nuclear polarity, and mitotic activity are distinctly more marked than in the benign papillary lesions Stromal invasion is also present (fig 39)

2. Colloid (mucoid) carcinoma. Secretion of mucin and even the occurrence of small foci of gelatinous character are not uncommon in otherwise ordinary breast cancers However, only those tumors in which mucoid change dominates the picture and is evident grossly should be classified as carcinomas of colloid type In our material, where they comprise about 1 per cent of the mammary carcinomas, they have been associated with a five-year survival rate approximately twice that of all mammary carcinomas The relatively favorable prognosis of this tumor type is a point of some disagreement Stewart (12), in particular, considers the colloid character of a carcinoma of the breast to have no prognostic

Fig 40 Colloid carcinoma A few groups of tumor cells are widely scattered in pools of mucin (×170)

significance Geschickter (18) is among those who consider the prognosis favorable Saphir (41) has suggested that a relatively low degree of malignancy is associated with the characteristic colloid carcinoma (described below) and that the disagreement stems from the classification of a variety of other tumors under the head of colloid carcinoma These include glandular tumors showing mucinous features which are not predominant as well as a highly malignant variant composed of signet ring cells Frantz (16) has presented data suggesting that those tumors in which intracellular mucicarminophilic material can be demonstrated have a more favorable prognosis than the average breast cancer Grossly the colloid carcinoma is usually soft and circumscribed presenting a homogeneous, translucent glairy cut surface (Plate IB) It may resemble a fibroadenoma with markedly myxomatous stroma but lacks the latter s distinct encapsulation Colloid carcinomas may attain considerable bulk before involving the axillary lymph nodes

The microscopic picture is one of pools of mucin separated from each other by more or less narrow fibrous trabeculae Groups of tumor cells often small and uniform and at times forming small tubules appear to float about in these pools The mucin, rather than the cells dominates the picture (fig 40)

3 **Medullary carcinoma with lymphoid infiltration** Moore and Foote (34) have used this designation for a sharply delimited morphologic type of breast carcinoma not in the non-specific sense of any soft or cellular, tumor Approximately 4 per cent of the mammary carcinomas we have studied may be placed in this classification. In this small material we have not observed any direct bearing on prognosis but the relatively favorable prognosis of

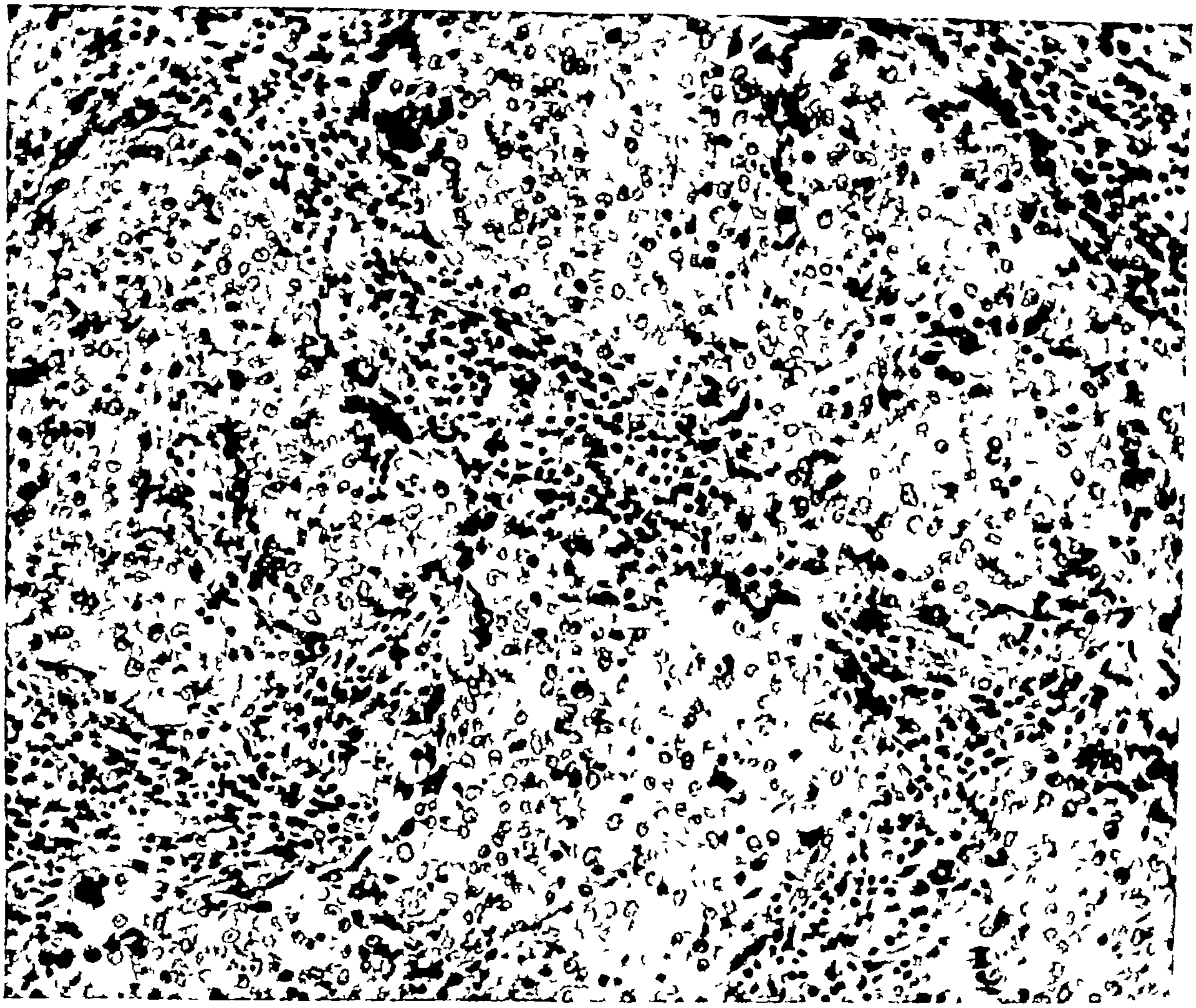

FIG 41 Medullary carcinoma with lymphoid infiltration of stroma (×195)

this tumor type seems clear from the data of Moore and Foote Forty-three (83 per cent) of their 52 patients were alive at the five-year interval, despite the fact that 22 (42 per cent) of the 52 had axillary lymph node involvement Grossly, the medullary carcinomas of this specific type may be bulky but, whether small or large, tend toward circumscription They are soft and cellular and not infrequently show areas of hemorrhage or necrosis Microscopically, they are seen to be composed of broad, anastomosing cords of large but fairly uniform cells with large vesicular nuclei and abundant cytoplasm Mitotic activity may be great, but pleomorphism is not marked Especially striking is the heavy lymphocytic infiltrate—at times so heavy as almost to obscure the epithelial nature of the neoplasm (fig 41)

4. Carcinoma of no special type. These are the common mammary carcinomas, comprising roughly 76 per cent of the total A dense fibrous stroma is a component of greater or lesser prominence and the tumors of this group are frequently labelled as scirrhous They are of indeterminate pathologic type so far as prognosis is concerned

We have not found the grading of mammary cancers to be of great value In general, grading is not helpful in determining the prognosis of the individual case although, in the analysis of large groups of tumors of some organs, histologic "grade" may tend to parallel the degree of malig-

nancy observed clinically The method is particularly limited with respect to the breast because so large a proportion of the cancers fall into the indeterminate group under discussion wherein wide variations in histologic appearance are encountered which, for the most part cannot be correlated with variations in clinical behavior Even so an occasional carcinoma may appear very anaplastic and demonstrate a correspondingly high degree of clinical malignancy Of far greater value in prognosis is the recognition of those specific morphologic types of carcinoma—intraductal papillary colloid and medullary—which we know to be associated with a better prognosis than the average (42) We know too that the inflammatory type of carcinoma (see below) and carcinoma arising during pregnancy or lactation, neither of which conforms to any particular histopathologic type are associated with a particularly bad prognosis (19) Within this group of carcinomas of no special type prognosis is best estimated on the basis of the extent of the disease, in particular the status of the regional lymph nodes, and on such factors as the size of the tumor diffuse invasion or relative circumscription multicentric or unicentric growth and the presence or absence of lymphatic blood vessel, nerve sheath or pectoral muscle invasion

Grossly the tumors of this indeterminate group are the typical breast cancers—they are hard and cut with increased resistance Their consistency has been likened to that of an unripe pear or raw potato The cut surface is usually grey presenting the characteristic yellowish 'chalk streaks' (Plate 1C) The periphery is irregular with radiating projections into the surrounding tissue giving a puckered appearance It is this penetration of the surrounding tissue, with the associated fibrosis, that produces the fixation signs which may be of diagnostic value (Plate 1D) Microscopically, these tumors tend to show greater variation than they do grossly The most frequently encountered appearance is one of moderate-sized fairly uniform cells growing in cords or broad columns and occasionally forming distinct lumina Mitotic figures may be very rare There are graded transitions from this picture to one of a very high degree of differentiation with well formed glands on the one hand and on the other to all degrees of highly cellular pleomorphic, anaplastic carcinoma The fibrous stromal component may be of any degree of abundance and density—varying greatly not only from one tumor to another but also from one area to another within a given tumor In general, the tumors in this group show the greatest fibrosis centrally and are more or less highly cellular in the peripheral zone of active growth (fig 42) A few infiltrating carcinomas are composed of small, uniform cells growing in narrow cords or penetrating the breast singly and showing no differential features These are regarded as of lobular origin by Foote and Stewart (13)

C Relatively Rare Carcinomas

Approximately two per cent of mammary carcinomas fall in this group which includes several morphologic sub-types

1 **Apocrine carcinoma** This type of tumor is characterized by the resemblance of the tumor cells to those of apocrine sweat glands and of the commonly observed apocrine metaplasia of the mammary ducts Although it is sometimes called sweat gland carcinoma it is a true carcinoma of the mammary ducts and should not be confused with carcinoma originating from the sweat glands of the overlying skin Grossly this tumor type has no specific identifying features Microscopically the tumors are composed of large cells with

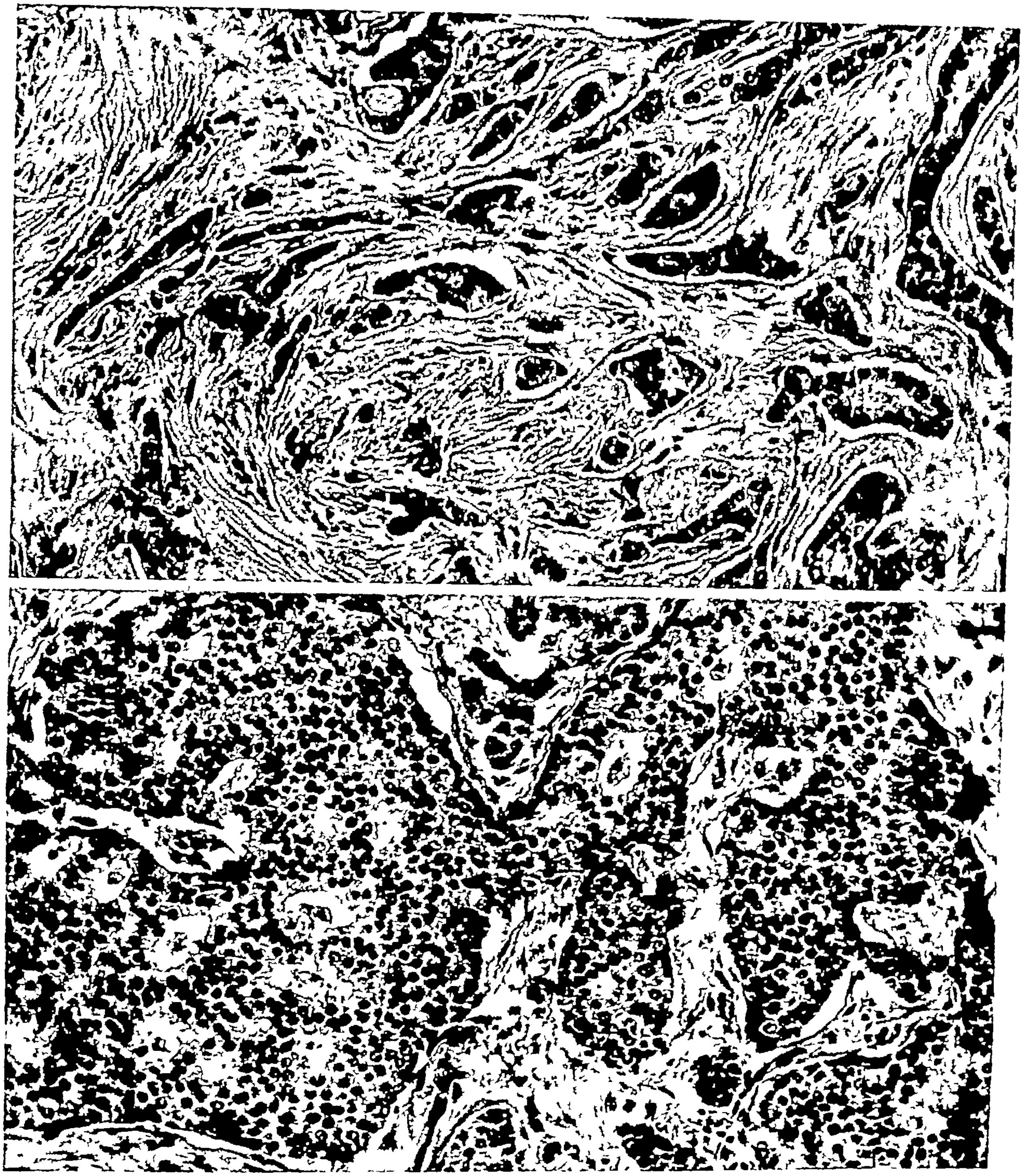

FIG 42 Carcinoma of breast of no special type The upper photomicrograph shows an abundant dense fibrous stroma whereas the lower illustrates a cellular portion of the same tumor (×195)

granular, eosinophilic cytoplasm, at times in a papillary pattern, simulating very closely the commonly observed apocrine metaplasia, save for the cellular pleomorphism and hyperchromatism and the invasive manner of growth (fig 43) There is no evidence that apocrine character has any bearing on clinical behavior or prognosis

2. Squamous cell carcinoma. Infrequently, a ductal carcinoma of the breast may undergo extensive squamous metaplasia, and at times the tumor may appear to be entirely squamous Stewart (42)

FIG 43 Apocrine carcinoma Note the large tumor cells with abundant pale granular cytoplasm (×225)

states that in his experience these tumors invariably include areas of transition from duct carcinoma We have seen squamous cell carcinomas which presented grossly as blood filled cysts the cyst wall being composed of tumor tissue

3 **Adenoid cystic carcinoma** Although small foci having this characteristic microscopic structure are encountered at times in duct carcinomas of the more common types the occurrence of tumors wholly of this pattern is rare. The author's material includes but a single case and Stewart states that his material contains only three Microscopically the tumor bears a very close resemblance to the so-called cylindroma of salivary and mucous glands (42) It is composed of rather small and uniform cells collected in masses within which are rounded spaces not readily identifiable as glandular lumina which contain a mucoid or hyaline material

4 **Carcinoma with pseudosarcomatous metaplasia** The tumors included under this heading are considered to be fundamentally of epithelial origin the sarcoma like areas, of undifferentiated spindle-celled tumor or of cartilage or bone, being metaplastic Frequently, the epithelial component is readily recognized but at times it may be necessary to examine many sections to demonstrate the carcinomatous nature of the tumor (fig 44) As a general rule the tumors in this group have been highly malignant and have pursued a rapid clinical course

D Paget's Disease of the Nipple

The disease described by Sir James Paget (40) in 1874 appears clinically as a weeping excoriated eczematoid lesion of

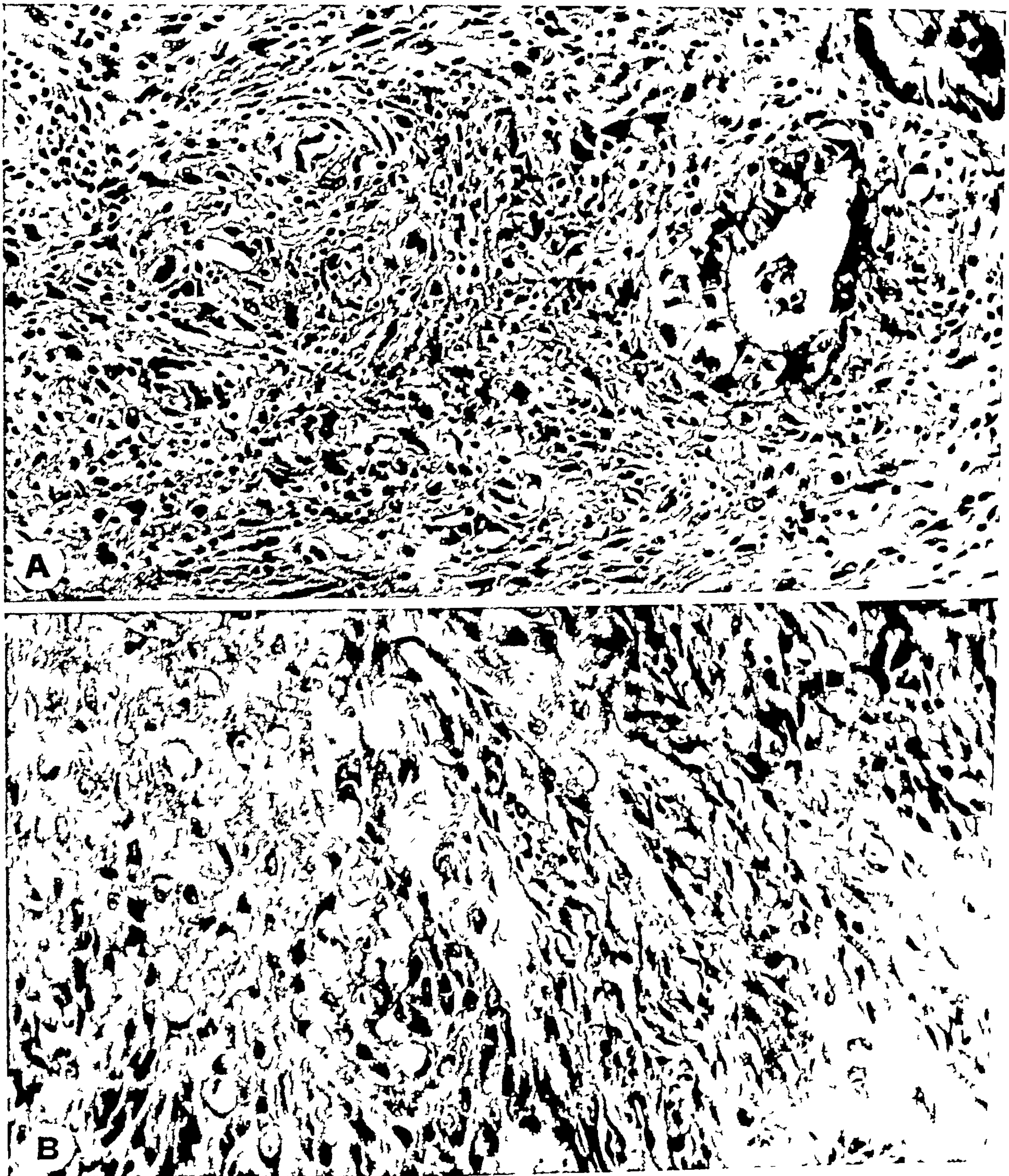

Fig. 44. Carcinoma of breast with sarcoma-like metaplasia. Upper, the tumor is largely one of spindle cells. Lower, cartilage and osteoid formation (×195)

the nipple which may progress to involve the areola and even the surrounding skin (Plate IIA). It is a manifestation of mammary cancer produced by spread from the lactiferous ducts to the epidermis of the nipple (36, 37). Not infrequently, Paget's disease is associated with carcinoma arising in the terminal part of the mammary duct system and the nipple changes are not accompanied by a palpable mass in the breast. Indeed, very meticulous pathologic study may be necessary to demonstrate the

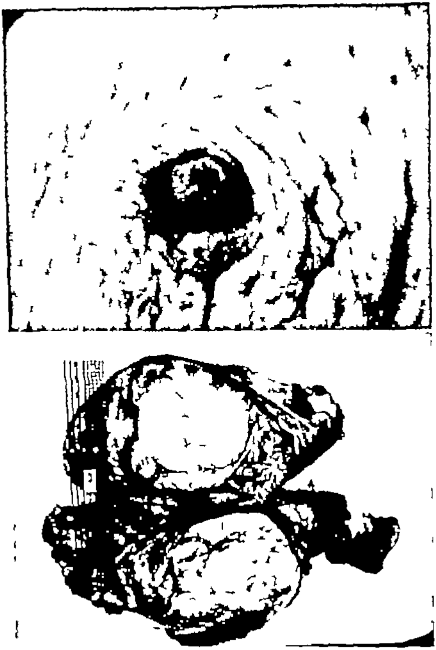

PLATE II

Above Paget's disease of the nipple Below cystosarcoma phyllodes. This tumor is benign.

underlying cancer Identical changes in the nipple may be produced in more advanced cancer by the same process (11) Paget's disease may be associated with axillary metastasis even when the primary tumor is not palpable Microscopically large, polygonal cells with pale cytoplasm and large, hyperchromatic nuclei are seen singly and in groups within the epidermis These are the so-called Paget cells and are identical with those of the underlying intraductal carcinoma (fig 45) In addition, inflammatory changes occur and the epithelium over the dermal papillae is thinned and may be eroded

A number of cases have been observed in this laboratory in which the so-called 'Paget cells contained yellow brown pigment presumably melanin In some cases the relationship of an underlying duct carcinoma to the nipple disease was readily apparent but when the tumor within the breast was small and difficult to find, differentiation between Paget's disease and intraepidermal malignant melanoma became a problem In each instance however intraductal mammary carcinoma could be demonstrated by careful study The carcinoma cells in the epidermis are believed to have acquired the pigment from epidermal melanoblasts otherwise identical tumor cells in the mammary ducts did not contain pigment

E Inflammatory Carcinoma

So-called inflammatory carcinoma of the breast is not a specific pathologic type of tumor but does represent a distinctive and dramatic clinical entity In this clinical form of mammary cancer the breast is diffusely enlarged indurated reddened and warmer than the opposite breast and the skin shows diffuse pigskin or peau d'orange edema. It must not be confused with a pyogenic infection or with focal inflammatory signs (erythema, etc) associated with a localized tumor The cancer cells spread freely and diffusely and invade dermal and subdermal lymphatics blocking them to produce the skin edema Associated capillary congestion accounts for the concomitant reddening and warmth of the breast completing the simulation of diffuse inflammation Systemic signs of inflammatory disease are minimal or lacking The cancer soon spreads beyond the breast pursuing a rapid and almost invariably fatal course About three to four per cent of breast cancers present this clinical picture They may be classified as primary or secondary In the primary cases the disease is of the inflammatory type from its inception whereas the secondary cases are those in which pre-existing tumors or tumors recurrent after treatment assume an inflammatory character and begin to grow and spread rapidly (26 43) Benign papillomas or the more usual varieties of carcinoma associated with true infection as well as infections alone may mimic this clinical picture Carcinoma associated with infection does not share the virtually hopeless prognosis of inflammatory carcinoma

II SARCOMA

1 *Malignant Cystosarcoma Phyllodes*

Cystosarcoma phyllodes is one of the many names (e g giant fibroadenoma, giant intracanalicular myxoma adenosarcoma) given to a specific type of mammary neoplasm which represents an alteration in the stroma of a fibroadenoma This stromal alteration is essentially one of increased cellularity and at times is indistinguishable from sarcoma Nevertheless the great majority of tumors labelled cystosarcoma phyllodes pursue a *benign* clinical course The tumor is usually large and frequently grows rapidly reaching a large size in a brief time There may be a history of a

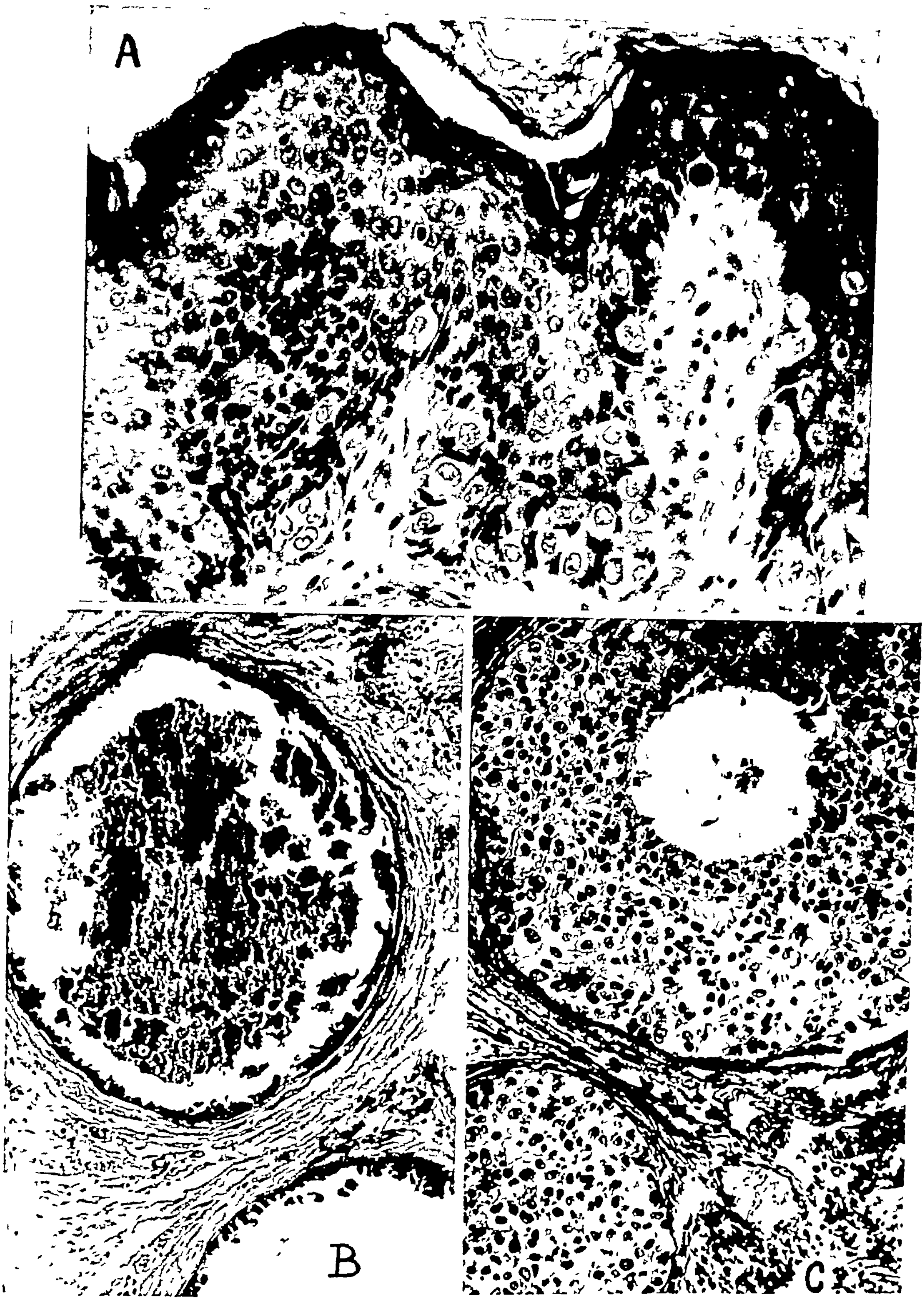

FIG 45 Paget's disease of the nipple Above, the so-called Paget cells within the epidermis (×285) Below, two different-appearing intraductal carcinomas, both of which were associated with Paget's disease The tumor on the left is of the type often designated as "comedo carcinoma" (×114)

FIG 46 Cystosarcoma phyllodes (benign) This was a very rapidly growing tumor The stroma is cellular but anaplasia and mitotic activity are not features (×195)

stationary or slowly growing tumor over a long period of time and then onset of rapid growth (27 44) Grossly the lesions are encapsulated and usually large, they may be either soft or firm section reveals lobulation and often cystic spaces into which project polypoid masses (Plate II B) Microscopically the pattern of the underlying fibroadenoma is generally recognizable. The epithelial elements play a passive role the difference from fibroadenoma being that of increased amount and increased cellularity of the stroma At times the cells may be enlarged and hyperchromatic but generally pleomorphism and mitotic activity are not important features (fig 46)

Despite the fact that most cystosarcomas are benign lesions a proportion behave as fully malignant neoplasms Treves and Sunderland (44) classified 18 (23 per cent) of the 77 examples they studied as malignant and another 18 as borderline These authors report focal sub-epithelial stromal cellularity and anaplasia as the earliest microscopic indication of malignant change and note that anaplasia and frequent mitoses were uniformly features of the malignant as opposed to the benign tumors (fig. 47) Metastasis was primarily by way of the blood stream

The data of Lester and Stout (27) attest to the rarity of the malignant variant of this tumor type supporting the suggestion of Treves and Sunderland that their series was weighted with malignant examples Lester and Stout also emphasize the difficulty amounting at times almost to impossibility of identifying the malignant tumors as such on histologic examination

FIG 47 Malignant cystosarcoma phyllodes The anaplasia is in contrast with fig 46, and mitotic figures are fairly numerous The mammary stroma was invaded in places This tumor metastasized to the lungs and skeleton (×195)

B Miscellaneous Sarcomas

Although rare, *fibrosarcomas* are the most commonly occurring of the soft tissue sarcomas in the breast *Liposarcomas* and *angiosarcomas*, as well as isolated examples of other connective tissue sarcomas, have been reported These tumors in the mammary gland do not differ from their counterparts occurring elsewhere in the soft tissues (22, 32) Lymphosarcoma (2), which may involve the breast in the course of generalized disease, may also occur as a primary tumor, metastasizing to the regional lymph nodes in the fashion of mammary carcinoma Morphologically, it does not differ from lymphosarcoma elsewhere in the body

Growth and Metastasis

Half of all mammary carcinomas occur in the upper outer quadrant of the breast About 20 per cent occur in the central portion of the gland and ten per cent in the lower outer quadrant The remainder, approximately 20 per cent, involve the medial half of the breast, more often the upper inner quadrant (table 3)

According to Nathanson and Welch (39) the average duration of life after the onset of breast cancer is 3 4 years for untreated cases and only 4 6 years for treated cases Cancer of the breast spreads in a variety of ways—within the mammary ducts, by direct invasion of contiguous tissues and by way of the lymph and blood vascular sys-

TABLE 8*

Site of Carcinoma

	Hospital of the University of Pennsylvania (10)	Ackerman & Regato (1)	Geschickter (18)
Center	12.5†	22†	22†
Upper Inner Quadrant	16.6	14	14.5
Upper Outer Quadrant	51.7	47	44
Lower Outer Quadrant	12	7	15.2
Lower Inner Quadrant	7.2	2	3.7

* From Boyd, Enterline and Donald (10).
† The figures are percentages.

tems. Spread within the mammary duct system is not of practical importance except in those instances when, early in the evolution of a cancer, it may be responsible for producing discharge from the nipple or the distinctive changes of Paget's disease of the nipple.

Direct invasion of contiguous tissues accounts for the fixation signs that may permit a clinical diagnosis of carcinoma—skin dimpling, nipple retraction, fixation to the pectoral fascia or muscle—as the accompanying fibrosis involves Cooper's ligaments (the fibrous septa that separate the mammary gland into its component lobes). Some mammary cancers, "medullary carcinoma with lymphoid stroma" and papillary carcinoma particularly, may attain a very large size without much infiltrative growth.

Tumor spread by way of the lymphatic system is of primary importance because of its bearing on the surgical treatment of this disease. Mammary carcinoma tends to invade lymphatic vessels at an early stage. Certain local changes may be the result of such invasion—as, for instance, "peau d'orange" or "pigskin" edema produced by blockage of dermal and subdermal lymphatics. Of especial significance, however, is the involvement of the regional lymph nodes by tumor emboli within the afferent lymphatics. Although there may be actual permeation of lymphatics in the immediate vicinity of a cancer, significant lymphatic spread is essentially a matter of embolization, lymphatic permeation (perhaps with retrograde spread) taking place only with very extensive involvement of the regional nodes. Nearly two-thirds of the breast carcinomas encountered in a general hospital have already spread to the homolateral axillary lymph nodes when the patient first comes under observation. The presence or absence of such involvement remains the single most useful criterion on which to base prognosis (see Chapter XIV). In our own studies, 75 per cent of patients without axillary disease survived five years, whereas only 31 per cent of patients with axillary lymph node involvement did so. The size of the tumor can be demonstrated to bear a similar relationship to prognosis—the larger the primary tumor the greater the likelihood of axillary spread and the poorer the prognosis. That clinical evaluation of the status of the axillary lymph nodes is highly fallible has been repeatedly demonstrated. Except in the case of patently widespread disease, therefore, it is incumbent upon the pathologist, examining a specimen from radical mastectomy, to dissect the axillary contents with meticulous care, removing all lymph nodes for sectioning and microscopic study.

The recent work of Handley (20) (see Chapter II) has revived interest in the internal mammary lymphatic chain and that of Andreassen and Dahl Iversen (3) in the supraclavicular lymph nodes. Tumors of the medial half of the breast metastasize by way of the internal mammary route more frequently than do tumors of the outer quadrants, but Handley and Thackray's data (table 4) indicate that this route is a secondary one and that, even when the

TABLE 4*

Site of Primary Growth

	Inner Half of Breast	Outer Half of Breast	Total
Total cases	61	89	150
All lymph glands free from growth	16	33	49
Axillary glands alone invaded	12	40	52
Internal mammary glands alone invaded	6	2	8
Both axillary and internal mammary glands invaded	27	14	41

* From Handley and Thackray (20)

tumor is centrally or medially placed, spread to the internal mammary nodes usually takes place only after axillary spread has impeded lymph flow by the primary axillary route

Andreassen and Dahl-Iversen (3) found unsuspected supraclavicular lymph node disease in 17 per cent of 98 cases in which routine dissection of the supraclavicular space was performed. This is 33 per cent of the cases in which axillary node involvement was present In every case where supraclavicular metastases were found, disease was also present in the axillary nodes McDonald, Haagensen and Stout (33) point out that when the subclavicular lymph nodes—the "highest" axillary nodes removed in the customary radical mastectomy—are involved, the carcinoma has usually spread beyond that point, beyond eradication by surgical means Therefore, it is important to include in the pathologic examination of the axilla a specific notation of the presence or absence of tumor in the lymph nodes from the apex of the axillary dissection This implies, of course, the labelling of the apical point of the specimen by the surgeon

In addition to the specific groups of lymph nodes referred to above, involvement of the nodes of the contralateral axilla and, less often, of the cervical nodes is not infrequently encountered

Finally, breast cancer is at times disseminated by way of the blood stream and, in fatal cases, distant metastases are frequently widespread Virtually any organ or system may be involved Among the sites of distant metastasis, the lungs and pleura are most frequently involved, the skeletal system and liver next. When skeletal metastases occur, they are usually found in multiple bones—the spine, pelvis, femur,

TABLE 5

*Frequency of Involvement of Various Organs by Metastatic Mammary Cancer**

	Willis (48) Autopsy Series (45 cases)	Warren & Witham (47) Autopsy Series (162 cases)	Boyd, Enterline & Donald (10) (Surgical Series) (417 cases)†
Lymph Nodes	80	71 9	
Homolateral Axilla			56
Homolateral Supraclavicular			20
Contralateral Axilla			7
Mediastinal			5
Cervical			4
Lungs	61	58	31
Pleura	42	39	
Liver	49	59	18
Bones	47	43	24
Spine			15
Pelvis			13
Femur			10
Ribs			8
Skull			5
Adrenals	20	32	—
Brain	16		4 1
Skin		40	9
Thyroid	18		
Kidney			
Peritoneum	13		

* The figures are percentages

† 135 (32 per cent) of 417 patients subjected to radical mastectomy did not develop demonstrable metastases during the period of observation—in no case less than 5 years

ribs and skull in that order (table 5) Batson (5) has demonstrated the importance of the vertebral venous system as a route for the dissemination of cancer in general With respect to mammary carcinoma this route of metastasis may well account for many instances of spread to the skeleton and brain

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CHAPTER VI

The Relationship Between Benign Breast Disease and Cancer

Introduction

Modern medical vigilance and early cancer detection require an accurate appraisal of the importance of benign breast disease and its relation to cancer The strength of such a study rests upon the weakness of our present modes of cancer diagnosis and therapy Does the significance of chronic cystic mastitis lie in the insignificance with which it is so often regarded? Should patients with fibroadenosis look forward to the future as a promise or as a threat? Can we accept with confidence the vacillating voices of pre-eminence, or must we fall back upon ill-defined and intangible clinical judgment the limitations of which are all too apparent in the candor of our own individual experience?

It is not uncommon for surgeons to recall a patient operated upon for a benign breast lesion—verified as innocent by pathologic examination—who some time later developed a carcinoma within the same breast Or many of us at least must certainly remember a patient with a small lump in her breast known to have been present for ten to 20 years before an increase in size compelled its removal for unforeseen cancer These striking examples of anatomic relationship might seem to be a link that is a little more than kin and a little less than kind Yet one must be extremely cautious in deriving probabilities based upon the principles of individual impressions The pitfall of this error lies within the very shadow of truth.

The importance of determining the relationship between benign and malignant breast disease is accentuated by the present challenge of the excessive toll taken by breast cancer We must know not only the value of early diagnosis and treatment but we must appreciate the relationship of predisposing factors in the development of breast cancer

Historical Review

The distinction between benign breast disease and cancer almost escaped recognition until the revelations of microscopic anatomy in the nineteenth century As noted by Goodall (16) in his carefully documented history of fibroadenosis the early Greek physicians, in spite of their keen observation of clinical syndromes left no record of their knowledge of benign breast disease

Among the medieval Renaissance and early modern surgeons and anatomists Guy de Chauliac (1300–1368), Fabricius (1537–1619) Vesalius (1514–1564) and Ambroise Paré (1510–1590), one finds many original descriptive illustrations of breast anatomy and several rather clearly defined accounts of carcinoma and breast abscess but the conception of benign breast tumors re-

mained dormant John Hunter (1728–1793) (18), a prolific writer, versatile surgeon and astute observer, recorded a giant fibro-adenoma as a case of "scrofulous breast, which came on at the age of 26, and increased gradually to 38 It was 16 or 18 pounds in weight In this case there was no disease leading to the axilla, as in cancer" In Hunter's "Lectures on the Principles of Surgery" delivered in 1786 and 1787, he distinguished between scrofula in the form of a benign breast tumor and cancer "If cancer, it will vary its appearance by becoming less circumscribed, not having so determined an outline, from the cellular membrane around becoming diseased, the skin will be less movable, the nipple more or less retracted, and the lymphatic glands going to the axilla will swell But in scrofula there will be no surrounding disease, no affection of the nipple or axillary glands, no adhesion, even though the tumour be large"

However, it was Abraham Colles (1773–1843) (7), a brilliant Irish surgeon, who first clearly defined benign breast disease in his "Treatise on Surgical Anatomy" in 1811 "Although the diagnosis between scirrhus and other diseases of the breast be not founded on the anatomical structure of this part, and consequently does not come within the scope of this work, yet I cannot refrain from stating the symptoms of another species of tumor, which is occasionally met with in the breast, as it is not described by any other author I have hitherto seen" An excellent clinical exposition of benign breast disease then follows which concludes with the hope "of preventing this kind of tumor from being mistaken for a true scirrhus"

Sir Astley Paston Cooper (1768–1841) (8), in his classical study "Illustrations of the Diseases of the Breast" published in 1829, divided breast lesions into three distinct classes (1) common inflammation—acute and chronic, (2) complaints arising from peculiar or specific action—non-malignant, and (3) malignant Non-malignant tumors were distinguished as "those which do not arise from a vitiated state of the system, nor produce any dangerous constitutional effects, and do not contaminate the parts in their neighbourhood, nor affect those at a distance from their original seat

"However, it is right to observe that some of these swellings, when they have existed long in a dormant state, will have alterations produced in them by changes of the constitution, by which their extirpation may be rendered necessary, for malignancy may be lighted up in them by constitutional disease—by anxiety of mind—and by the cessation of the menstrual secretion" Later, in his introduction to "The Anatomy and Diseases of the Breast" (1840), Sir Astley Cooper (9) reviews the resemblance between non-malignant and malignant "affections" and comments that "these abnormal growths (non-malignant), although they might simulate with such morbid changes in some of their characters and symptoms, yet differ from them (malignant) in their progress, in the treatment which they required, and in the probability of a fatal termination"

Velpeau (1795–1867) (30), a great teacher with opportunities for tremendous clinical experience, recorded his diligent observations in "A Treatise on the Diseases of the Breast and Mammary Region" which was published in 1854 In the differential diagnosis between cancer and innocent breast tumors, Velpeau comments on the transformation of tumors "If it were shown that cancer were only the ultimate state, the transformation of tumours originally innocent, a more minute examination, a more extended semiology would be useless, but as has already been seen, if the possibility of certain transformations cannot be denied, it is at any rate

incontestable that they are rare' In conflict with the prevailing views of Lisfranc whose contrasting opinion maintained that every tumor of the breast led to cancer, Velpeau 'laboured incessantly to remove from the category of cancers different tumours which do not belong to it.'

Sir James Brodie (3) in his "Lectures on Pathology and Surgery" (1846), regarded cystic tumors as benign but did not preclude the possibility of the development of carcinoma He called attention to the recurrence of these multiple benign cysts if the entire mammary gland was not removed In 1883 Reclus (26) made a comprehensive clinicopathologic study of "cystic disease of the breast" and his description of this syndrome is tenable today He considered benign lesions as multiple, bilateral not associated with cachexia or lymph node enlargement non tender smooth and without fixation thus differing from malignant lesions. Since one can neither foretell or prevent the possibility of cancer development in older patients with cystic disease" Reclus recommended the removal of the diseased breast The exhaustive histologic studies of Brissaud (1884) (2) attached *great significance to epithelial proliferation* This served as a stimulus for similar cytologic investigations by Schimmelbusch (1890 1892) (27 28) in Germany, which resulted in calling adenosis or adenoma with cyst-formation, 'Schimmelbusch's disease' a most unwieldy and ponderous name König (1893) (20) on the contrary christened the lesion chronic cystic mastitis in the belief that epithelial proliferation and inflammatory interstitial changes were the result of a vicious cycle of secretion and irritation

Since so panoramic a study is contingent upon so many perplexing problems and so much doubtful data there has accumulated a vast and still quite vague accounting of this clinicopathologic subject in the medical literature The comprehensive resumés of Semb (29), Campbell (4), Foote and Stewart (13), Cheatle and Cutler (5), Patey (24), Klingenstein (19) and Warren (31) are authoritative compendiums of work and wisdom, past and present which have nourished this branch of the tree of knowledge That the current conception regarding the relationship between benign breast disease and cancer is dependent upon the most divergent data can best be seen by the statistical analysis summarized in table 6

Classification of Benign Breast Disease

In a study of benign breast disease it is often a desirable gambit to begin by defining one's terms. For no matter to what precision one may aspire, in a clinical investigation of benign breast lesions one is constantly handicapped by a barrier of conflicting and complicated terminology Benign breast disease enfolds in its indiscriminate embrace a galaxy of synonyms all of which are in common use and many of which describe what may actually be the same lesion Thus, we are often confronted with a potpourri of terms which include fibroadenosis, fibrocystic disease chronic cystic mastitis mastopathy *nodular hyperplasia*, cyclomastopathy adenofibromatosis papillomatosis Reclus disease Bloodgood's blue-domed cysts Schimmelbusch's disease mazoplasia cystiphorous epithelial hyperplasia, chronic mastitis mammary dysplasia, mastodynia adenosis adenocystic disease and several other complex and hybrid names These are often repeated in the literature thus adding chronicity to confusion

Foote and Stewart (13), in their scholarly study of cancerous versus noncancerous breasts do not favor 'the term 'chronic cystic mastitis in the diagnosis of lesions of the breast since it conveys no indication of the presence or absence of many characteristic histopathologic changes moreover it

TABLE 6

Collective Review of the Relationship Between Benign Breast Disease and Cancer

No	Author	Year of Publication	Type of Diagnosis	Total No of Cases	Per Cent Followed	Follow-up Period	Per Cent of Cases Followed Developing Cancer	Remarks
1	Schimmelbusch	1890	Pathologic	43		None	7	Co-existence of cancer and benign breast disease
2	Speese (Personal)	1910	Pathologic	35		None	26	Co-existence of cancer and benign breast disease
3	Speese (Collected)	1910	Pathologic	295		None	15	Co-existence of cancer and benign breast disease
4	Greenough and Simmons	1914	Pathologic	102	81	1 to 17 years	4 8	59 patients out of 83 had a partial resection and 32 patients had a local excision Average follow-up period 7 years
5	Bloodgood	1921	Pathologic	128			2 4	Follow-up period and number of patients followed not stated
6	Johnson	1924–25	Pathologic and Clinical	107	61	1 to 20 years	1 9	Cystic disease alone considered
7	Semb	1928	Pathologic	144		None	17	Frequency of cancer in pathologic examination of primary fibro-adenomatosis
8	Oliver and Major	1934		106		5 plus years	1	
9	Campbell	1934		190	62	5 plus years	0 5	Simple cystic disease
10	Campbell	1934		42	52	5 plus years	0	Adenocystic disease
11	Klingenstein	1935	Pathologic	226	24	2 to 11 years	3 7	Patients upon whom only partial breast excision was done
12	Warren I	1940	Pathologic	1206		Average 9 years	3 5	Aggregate cases including chronic mastitis, chronic cystic mastitis, cystadenomas, adenomas, in all cases
13	Warren II	1940	Pathologic	604	67	Average 9 plus years	4 9	Massachusetts cases alone Chronic mastitis—173 Chronic cystic mastitis—340 Cystadenomas—21 Adenomas—70 Cancer—30
14	Warren III	1940	Pathologic	602		5 plus years in ⅔ of cases	2 0	Toronto cases alone Chronic mastitis—128 Chronic cystic mastitis—403 Duct papilloma—71 Cancer—12
15	McKinley	1943	Pathologic	60	47	1 to 10 years	0	Average follow-up period only 3 years
16	Clagett et al	1944	Pathologic	442	86	5 to 6 years	1 8	Short term follow-up from Mayo Clinic
17	Geschickter	1948	Pathologic and Clinical	793		5 to 30 years Average 10 plus years	1 3	Mastodynia 231, Cancer in 0 Adenosis—184, Cancer in 6 Cystic diseases—378, Cancer in 4
18	Atkins	1950	Pathologic and Clinical	326	78	1 to 14 years	0 8	Material from Mastitis Clinic of Guy's Hospital All cases called fibroadenosis
19	Lewison and Lyons	1953	Pathologic	451	85	1 to 25 years	1 8	Average follow-up period of 13 6 years with 75 per cent of all patients being followed from 10 to 25 years

implies a common etiology for a variety of lesions, most of which are anything but basically inflammatory processes" However, they concede that "the term 'chronic cystic mastitis' is so ingrained in the minds of some pathologists that this diagnosis of a locally excised portion of breast almost amounts to a surgico-pathologic reflex Such haphazard terminology leads to neglect of the actual lesions, even though it may

enforce the employment of a rather complicated terminology."

Nevertheless the present opinion of American physicians is biased in favor of the term chronic cystic mastitis (in Great Britain the term "fibroadenosis" appears to be preferred). Although a term should not be considered correct merely because it is useful, yet chronic cystic mastitis is a byword of expediency because it is accepted by all, advocated by authority, and recommended by custom. Preference is given in this discussion to (1) *chronic cystic mastitis* the all inclusive clinicopathologic complex with characteristic lesions of gross or microscopic cysts (2) fibroadenoma, the diffuse or localized proliferation predominantly of fibrous tissue and (3) papilloma the proliferation and papillary hyperplasia of epithelial elements. Ductal epithelium may reveal plication layering and great cellular variability without nuclear changes characteristic of cancer.

It is essential to point out that this and all other classifications of benign breast disease are based upon the predominant pathologic picture. In many cases the pathologic appearance is characteristic, in part at least of two or more types of abnormality. Rarely does the lesion consist entirely of a single pathologic pattern. The routine practice of Cheatle and Cutler (5) of examining microscopic sections of whole breasts "definitely proves that it is unsafe to assume that sections made from only part of the breast represent the state of the whole gland."

Evidence of Relationship

The earliest studies of the relationship between benign breast disease and cancer were primarily descriptive and speculative. More recent investigation is based upon evidence that is experimental histological and clinical (or statistical).

Experimental

Breast cancer can be produced in mice and rats (see Chapter IV) by intensive and prolonged estrogenic stimulation. The pioneer studies of Goormatigh and Amerlinck (17) discovered the cystic changes which occur in the castrate female mouse breast after prolonged estrogen (follicular) stimulation. The development of cancer occurred in one out of 11 mice of an impure stock. These authors concluded that the parallelism between the lesions of benign breast disease in the human and in the mouse was "quasi complet." The classical work of Lacassagne (21) indicated that changes characteristic of benign breast disease are often a precursor to breast cancer produced in response to estrogenic stimulation of mice. Geschickter (15) has demonstrated that various initial changes such as cyst formation and the development of fibroadenoma may also occur in the rat in response to prolonged and intensive estrogenic stimulation. Although these changes characteristic of benign breast disease are not necessarily essential to the subsequent development of breast cancer, yet they do occur in response to the administration of estrogens. The cystic and proliferative changes produced in experimental animals in response to an abnormal hormone environment are similar to changes characteristic of benign breast disease in the human. Certain investigators have demonstrated varying degrees of hyperestrogenism (depending on age) in human breast cancer.

Pullinger (25) points out that Lett in 1905, speculating on the relation between ovarian secretion and chronic mastitis wrote "Carcinoma as is well known not infrequently develops in a breast which is already the seat of a chronic mastitis, and it may be that there is a connexion between the secretion of the ovary one or more of the varieties of chronic mastitis, and mammary cancer

In a distinguished group of carefully conducted experiments Pullinger demonstrated that estrogen alone could produce adenosis with duct-acinar distention and secretion without the combined action of progesterone or prolactin. These changes in mice were independent of the milk-factor, failure of involution, or of breast cancer. It is the opinion of Pullinger "that the capacity to react by cystic dilatation combined with adenosis-like proliferation, which is hereditary in certain strains (of mice), is not correlated with the hereditary factor which underlies susceptibility to cancer." In certain respects this idea substantiates the belief of Cheatle and Cutler (5) that benign breast disease in humans begins as an independent entity, quite apart at the start from cancer, yet a chain of events may ultimately lead to the transition of hyperplasia to neoplasia. In studying the problem of where and how the steroid hormones interfere with the dynamics of cancer, Lipschutz (23), working with guinea pigs, found that adenocarcinoma of the breast never developed in these animals despite prolonged administration of estrogens. Fibroadenomas of the breast occasionally occurred but these tumors were much less striking than the estrogen-induced fibroids within the abdominal cavity.

Much of the preceding experimental essay has one serious defect in common, all conclusions are based upon experimental research with small animals. Although Pullinger (25) considers both human and experimental cystic disease as comparable and brought about by an excess of estrogens, yet the decisive factor in each case is the atypical response of the target tissue. Perhaps as suggested by Foote and Stewart (13), "the physiologic gap between the two species is too wide for mutual transposition of morphologic observations." However, the failure to produce experimental breast disease or tumors in a primate, the Macacus rhesus monkey, after years of continuous estrogen administration adds to the caution of transposing results from one species to another.

Although the critical role of the steroid hormones has been sufficiently demonstrated in the pathogenesis of breast cancer in some rodents, yet a systematic clinical study by the members (10) of the Committee on Research of the Council on Pharmacy and Chemistry of the American Medical Association, concerning the effects of massive and prolonged estrogen therapy in patients with advanced or metastatic breast cancer, has revealed neither the induction of benign breast disease or secondary breast cancer in these postmenopausal women in excess of what might be expected. Even after several years of intensive therapy with estrogens and/or progesterone, biopsy specimens of breast tissue and clinical examination in these postmenopausal patients reveal relatively few histologic changes characteristic of benign breast disease. However, the development of gynecomastia with proliferation of all epithelial elements which occurs following prolonged estrogen administration for prostatic cancer is highly suggestive of specific target organ tissue growth. The untoward development of breast cancer in the male as a result of exogenous estrogens is fortunately very rare, but this local manifestation of an upset hormone balance is a conversion of considerable importance.

Histologic

The best proof of the causal relationship between benign breast disease and cancer would be the simple and direct histologic demonstration that the point of departure in breast cancer begins in a nidus of benign breast disease. Although Foote and Stewart are at a loss for precise figures, they state, "We can confidently say that we have seen cancer begin *in duct papillomatosis, solitary*

and multiple, cyst, apocrine epithelium and blunt duct adenosis.'

Campbell (4) has carefully reviewed the literature and found many exponents of the "evolutionary" theory of benign breast disease in which simple cystic processes gradually assume more and more hyperplastic forms, passing imperceptibly from benign to malignant breast tumors Cheatle and Cutler (5) describe 'desquamative epithelial hyperplasia wherein cysts are formed which may pass gradually from benign to malignant hyperplasia or neoplasia Ewing (12) found precancerous changes in a number of breasts removed for benign disease Increasing epithelial overgrowth was considered the forerunner of breast cancer in at least some cases originating in an area of cystic disease

Among some investigators there appears to be a certain positiveness in their belief in the evolution of epithelial hyperplasia to neoplasia. By believing most that which is understood least they may become a heretic to the truth However Atkins (1) is more circumspect about the charm of these histologic inventions Histologically the game of arranging a number of microscopic slides in a series showing a normal breast at one end of the scale, all the intermediate phases of fibroadenosis in the middle and cancer at the other is one which few histologists can resist playing Yet the sequence of such evidence merits most serious consideration and the ridicule of reductio ad absurdum by showing 'that the normal breast develops from carcinoma through all stages of fibroadenosis in the reverse order" is hardly a test of truth In the opinion of Atkins one of the most important 'fallacies in the histologic argument" is that it fails to take into account the striking fibrous-tissue reaction which accompanies the epithelial changes and which has no part in the stimulation of cancer and may indeed be inimical to it It is possible, however that this superfluous fibrous tissue response may be but a "monument of mutability" in the body's effort to safeguard itself against the ravages of an unknown and invisible pathogenic force Such a teleological concept is unacceptable to Atkins because it is "incapable of either proof or disproof"

Benign prostatic hypertrophy has been frequently suggested as a precursor of prostatic cancer and the subject has been the source of considerable discussion in the medical literature If a direct etiological correlation is not tenable on the basis of histologic evidence alone the association might, perhaps, be explained as the result of a common antecedent factor or inciting agent Edwards Steinthorsson and Nicholson (11) found that a statistically significant relationship could be demonstrated between prostatic cancer and benign hyperplasia although the precise nature of this relationship remained obscure

Campbell has summed up the histologic evidence presented in favor of the precancerous theory of benign breast disease

1 Cystic disease is frequently found in association with *frank carcinoma*.

2 Various gradations of epithelial proliferation may exist to give the impression that cystic disease represents a progressive evolution of epithelial hyperplasia eventuating in carcinoma.

Clinical

With the many misgivings of microscopic evidence as well as the limits of information contingent upon present experimental methods perhaps the most practical and direct approach to the problem is the clinical follow-up technique. Does cancer follow benign breast disease in a higher *proportion* of patients than in the normal population? What is the clinical behavior of a benign breast lesion over the course of years and

how is its histologic appearance related to follow-up results?

Statistics, it is said, are no substitute for clinical judgment. Yet in the absence of reliable diagnostic criteria for benign breast disease (it is clinically difficult to determine a precise time of onset), our lack of knowledge must not lead to complacency. Seasoned statistics are the scaffold of experience upon which is built sound clinical judgment. At present the most reliable method of determining the relationship between cancer and benign breast disease is the long term follow-up of a substantial group of patients.

Over the course of years there have appeared many and varied reports (table 6) on the tendency of cancer to follow benign breast disease. In some, the method of the study was responsible for the character of the confusing conclusions. Perhaps a large number of patients were "lost" to follow-up, or the early age at operation, or the trifling time of follow-up, may have made the results unworthy of serious consideration. The validity of the diagnosis, clinical or pathologic, was often found wanting or scarcely substantiated by sound scientific evidence in so controversial a subject. Nevertheless, there is sufficient competent evidence to indicate that a positive relationship exists between benign breast disease and cancer. However, there are no decisive studies favoring one specific type of benign breast lesion over another as being particularly precancerous.

In a unique follow-up study Foote and Stewart reviewed the records of 1200 cases of operable breast cancer and found a previous history of benign breast disease (confirmed by operation) in 2.4 per cent. For control purposes the records of 1200 cases of cancer elsewhere in the body were reviewed. Of these 1200 cases of non-breast cancer only 1.08 per cent had a previous history of benign breast disease (confirmed by operation). It is of particular interest to note in their discerning commentary that only a ten year follow-up period would have been insufficient to show the development of seven out of 12 cases of breast cancer.

Lewison and Lyons, Jr. (22) have reported a long term follow-up survey of all patients who were operated upon at the Johns Hopkins Hospital for benign breast disease during the period 1925 through 1941. Each patient was a hospitalized "bed-patient", and the validity of the diagnosis was based upon pathologic evidence obtained in the operating room by use of the scalpel rather than by the random probing of an aspirating trochar. Whereas these patients requiring surgery may represent a selected sample of more severe benign breast disease, yet the results of clinical investigations of unconfirmed cases (clinical diagnoses alone) have been a common source of inaccuracy in otherwise reliable studies of a similar nature.

Between 1925 and 1941 inclusive there were 451 patients operated upon at the Johns Hopkins Hospital for benign breast disease (table 7). This period was especially chosen to allow most patients under survey to approach or actually reach the so-called "cancer age". Obviously, this latent period alone has inevitably increased the difficulties of patient follow-up and consequently decreased the number of patients successfully followed. Nevertheless, a total of 385 patients were finally accounted for, thus completing an 85.4 per cent follow-up over a one-to-25-year survival span.

Follow-up information revealed that of the 385 patients with benign breast disease who were successfully contacted there were 271 white women and 114 Negro women. The operative site was right-sided in 192, it was left-sided in 179, and it was bilateral in 14. There appeared to be no significant differences in the several categories of benign

TABLE 7

Comparison of Patients Followed and Patients Unable to be Followed

	Patients		Place of Residence				Status			
			Baltimore and vicinity		Not local		Privat patients		Clinic patients	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Followed	385	85 4	237	62	148	38	135	35	250	65
Unable to be followed	66	14 6	24	36	42	64	34	52	32	48

breast disease as indicated by the following data

	White	Negro	Right	Left	Bilateral
Fibroadenoma	178	72	96	95	0
Chronic cystic mastitis	124	29	83	65	5
Papilloma	19	13	13	19	0

The operation of choice was predominantly that of simple excision which was performed in 92 per cent or 352 patients However in the patients with papilloma where there was apt to be marked or moderate epithelial hyperplasia a more extensive operative procedure was often chosen as indicated by the following data

	Operation		
	Simple excision	Simple mastectomy	Radical mastectomy
Fibroadenoma	196	4	*0*
Chronic cystic mastitis	133	17	3
Papilloma	23	6	3

Since 8 per cent of the patients under survey were subjected to mastectomy it is perhaps proper to assume that the over all chance of these pateints with one breast amputated (there were no patients with bilateral amputations) to develop cancer at a later date might be slightly less than a similar group of normal women However the not infrequent finding of breast tissue within the operative field following simple mastectomy is unequivocal evidence that such an assumption is not entirely correct or justified Indeed it was the *irony of fate* for one recent patient (not in the reported survey) to develop breast cancer within the *scar of a simple mastectomy* Also benign breast disease is most often a diffuse and bilateral process

Arranging the ages at operation into quinquennial periods (table 8), the maximum incidence for fibroadenoma was found to be *between 21 and 25* for chronic cystic mastitis between 41 and 45 and for papilloma between 46 and 50 The average age at onset *was 30 for* fibroadenoma, 42 for chronic cystic mastitis and 47 for papilloma This coincides with the observations of many *other investigators* and clearly indicates the average age difference of these three types of benign breast disease Although the peak *incidence* between benign breast disease and breast cancer may be some years apart there is considerable overlap in the age *distribution* of both types of diseases

Benign breast disease recurred in 50 out of 385 patients thus manifesting a recurrence rate of 13 per cent It is not plausible to expect that the local excision of a single area of benign breast disease in a lesion *notorious* for its diffuse and widespread characteristics would result in a complete and permanent cure Warren (31) noted a

TABLE 8

Age Distribution

Benign Breast Disease	Age											Total Patients
	<20	21–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	65+	
Fibroadenoma												
At onset	36	48	33	29	21	18	9	3	2	1		200
At end of follow-up	0	0	17	29	43	29	33	15	20	9	5	200
Chronic cystic mastitis												
At onset	4	7	9	15	28	39	36	4	5	2	4	153
At end of follow-up	0	0	3	5	6	16	17	30	33	25	18	153
Papilloma												
At onset	0	2	0	5	6	3	7	2	1	3	3	32
At end of follow-up	0	0	0	0	2	4	5	5	5	3	8	32

15 per cent recurrence rate in patients with "chronic mastitis" and a 17 per cent recurrence rate in patients with "chronic cystic mastitis." When considering this perplexing disease, the diagnosis of which is so often confused by variable signs and symptoms, it is rather to be anticipated that the opposite breast (composed of identical target organ tissue) would be frequently the site of recurrent benign disease. The surprisingly infrequent recurrence of papilloma in the reported series is indicated by the following data:

	Recurrence—Benign Breast Disease		
	Same breast	Opposite breast	Bilateral
Fibroadenoma	6	8	7
Chronic cystic mastitis	8	11	8
Papilloma	1	1	0
Total	15	20	15

A total of 7 patients (1.8 per cent) out of 385 developed breast cancer (table 9). In all seven of these patients subsequent surgery was performed and the diagnosis of cancer was confirmed by microscopic examination. Although no delay in this condition could be too long, yet the latent period between benign breast disease and cancer varied from six to 18 years. A simple surgical excision was the primary operative procedure in all patients. Of special interest in these statistics is the development of cancer on the side opposite the primary breast disease in four out of seven patients.

Evaluation of Statistical Evidence

An appraisal of the foregoing results is predicated upon several major premises. It must be assumed in the first place that the removal of a benign breast lesion by simple surgical excision (as occurred in 92 per cent of the reported patients) did not necessarily eradicate all of the abnormal tissue. In a disease where the borderline between normality and abnormality is at best an indefinite one, it is impossible to say "how many alveoli per square millimeter of cross section of breast tissue is to be regarded as normal for any particular age or physiological state of the breast." Underscoring the validity of this statement is a valuable study by Stout as reported by Frantz et al. (11). So-called chronic cystic mastitis was found by this surgical pathologist in 71.4 per cent of 1038 surgical pathologic breast specimens. Some

TABLE 9

Results of Present Study

Benign Breast Disease	Number of Patients	Average Age at Onset	Average Duration, Follow up	Recurrent Benign Disease		Developed Cancer	
				Number	Per cent	Number	Per cent
			yr.				
Fibroadenoma	200	30	14 1	21	10 5	3	1 5
Chronic cystic mastitis	153	42	13 3	27	17 6	4	2 6
Papilloma	32	47	11 3	2	6 3	0	0 0
Total	385	36	13 6	50	13 0	7	1 8

degree of chronic cystic mastitis was also noted in other parts of the breast in 78.5 per cent of 410 cases of breast cancer In a long and comprehensive monograph by Semb (29) fibro-adenomatosis was noted in 77 per cent of 122 cases of breast cancer Fibro-adenomatosis was diffusely distributed throughout the entire breast tissue in 33 per cent of all cases In the survey of Foote and Stewart, by using 'the presence of at least one of the cystic or proliferative lesions as a standard for the diagnosis of so-called chronic cystic mastitis this condition is found in 59 per cent of the 300 cancerous breasts and in 65 per cent of the 200 non cancerous breasts

A major contribution to this problem was recently made by Frantz and her colleagues In a special study of the breasts of 225 routine cases coming to autopsy in whom there was no history of previous benign or malignant breast tumors these investigators found a high incidence of benign breast disease The ages ranged from 13 to 88 years and none of the cases were pregnant or lactating at the time of death The incidence of chronic cystic disease in these 225 cases of so-called normal breasts was found to be 53 per cent This was a significantly lower incidence than is usually found in breasts removed for cancer Gross evidence of cystic disease was actually noted in 19 per cent of the cases The incidence of benign breast disease as determined by clinical examination alone is known to be considerably lower Thus, it appears unlikely that simple surgical excision could possibly eliminate all or even most of the abnormal tissue of benign breast disease

An analysis by Montgomery, Bowers and Taylor of the clinical records of 4 651 patients seen in a busy obstetrical and gynecologic office practice, recorded a total of 24 527 breast examinations There were 479 disturbances of the breast noted The most commonly observed benign lesion was chronic cystic mastitis or fibrocystic disease in 295 cases Fibroadenomata was present in 32 cases intraductal papilloma in 14 cases, mastodynia in 32 cases and a number of miscellaneous clinical conditions were also noted Cancer occurred in 32 cases The incidence of benign breast disease in this clinical series of routine examinations therefore approached 10 per cent of all patients

The second assumption as suggested by Warren that must be seriously considered is that the same hormonal imbalances which could conceivably have been responsible for the primary benign breast disease would have the opportunity of continuing to influence the residual breast tissue The validity of this proposition is best demonstrated in our reported study (22) by the 13 per cent recurrence rate of patients requiring subsequent breast surgery for benign disease The

TABLE 10

Summary of Seven Patients Developing Breast Cancer

	No	Primary Operation	Side of Primary Operation	Age at Onset	Age Developed Cancer	Interval Benign Disease to Cancer	Side Cancer Developed
						years	
Fibroadenoma	1	Simple excision	Right	29	47	18	Left
	2	Simple excision	Left	54	62	8	Left
	3	Simple excision	Right	31	49	18	Right
Chronic cystic mastitis	4	Simple excision	Right	42	51	9	Left
	5	Simple excision	Right	45	55	10	Left
	6	Simple excision	Right	40	51	11	Left
	7	Simple excision	Bilateral	38	48	10	Left
Papilloma	None						

incidence of recurrence appeared greatest in the opposite breast, yet bilateral recurrences were not at all uncommon The development of cancer in the opposite breast as often as in the breast requiring primary operation for benign disease adds confirmation to this concept

Lastly, if benign breast disease is to be considered a precancerous condition, then the relative incidence of ultimate breast cancer in our series should be higher than the incidence of breast cancer in the normal population The problem of determining this incidence over a long period of follow-up in the normal population for the purpose of proper comparison is not an easy matter However, by using several different methods of computation the chances of acquiring breast cancer (expected incidence), in this group of relatively young women with benign breast disease followed for an average period of 13 6 years, was carefully determined The real incidence, as indicated in table 10, proved to be 2 6 to 3 6 times as great as the expected incidence Similar studies by Warren (31) in Boston and Clagett (6) at the Mayo Clinic indicated a striking correlation of results The breast cancer incidence for women with pre-existing benign breast disease was 4 5 times as great as expected in Warren's series and five times as great in Clagett's series Thus, the results of several clinical follow-up studies reveal that women with benign breast disease actually do have a limited but distinct predisposition to develop breast cancer if compared to normal women of a similar age range

It seems a safe and salutary scheme to suggest that all patients with benign breast disease be examined at periodic intervals The efforts of cancer control groups toward educating all women in the importance and technique of self-examination (see Chapter XVIII) are particularly praiseworthy Regardless of the individual interpretation of existing evidence there appears to be a basic relationship between benign breast disease and cancer Present knowledge indicates a small but firm core of common agreement on this subject, surrounded by a wide variety of individual differences of opinion Certainly, the experimental evidence is strongly suggestive, the histologic study is apparently indicative, and the clinical statistics are perhaps the most impressive, albeit the precise importance of benign breast disease as a precursor of breast cancer depends upon the still unpenetrated cause of these diseases Yesterday's yardsticks for the detection and diagnosis of breast pathology

may have been too yielding Perhaps future wisdom will forgive our present clumsiness and in the full light of tomorrow we will be able to look forward toward the conquest of both benign and malignant breast disease Until then however the teachings of Sir Astley Cooper (1829) (9) still serve as our surest safeguard and the source of inspiration "Though no specific remedy may yet have been discovered for the cure of some diseases it is still a great advantage to be able to discriminate curable from incurable cases, the dangerous from the slight those which require surgical operations from those which do not demand them and such as admit of a trifling operation from those which call for one of extreme severity"

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CHAPTER VII

The Psychological Aspects of Breast Cancer

The approach to any illness as serious as breast cancer which does not consider the psychological or social aspects of the patients as a human being but tends to treat only the organ or the disease reduces the practice of medicine from a professional art to a technical skill. A deep and sincere interest is required in dealing with people if the art of human relations is to be successfully practiced. Respect for the personality of the patient is the first and foremost requisite which will undoubtedly enrich even the most meticulous mastectomy in the treatment of this grave disease.

In cancer it is a tenet of truth that turmoil of tissue at the cellular level will seriously disrupt the tranquility of life at the clinical level. Combining the facts of science with the more spiritual requirements of the patient is in essence the art of the practice of medicine. Whereas the enormous advances of pure science have overshadowed the psychologic aspects of medicine, in a patient with cancer there is a unique opportunity for the blending of these dual disciplines. Although psychologic understanding does not directly affect the course of breast cancer as we now know it, yet it can be of considerable practical value to the physician in his handling of many problems of gravest concern to the patient.

In devoting ourselves to the *total care* of breast cancer we must consider the patient as a human being suddenly subjected to the stress and strain of a relentless malignant disease. By trying to evaluate the meaning of both the disease and the organ of its origin in each individual patient, it is possible for the physician or surgeon to function in a major supporting role. This will, of course, add considerably to the patient's well being.

Thou must be like a promontory of the sea against which, though the waves beat continually, yet it both itself stands and about it are those swelling waves stilled and quieted.

Emotional reactions may vary from patient to patient depending to a great extent upon many factors. Yet despite a constantly shifting pattern of individual behavior, a single patient will tend to exhibit a rather consistent trend of personal reactions although the details may differ from time to time. Similar over-all patterns are universally present, but the specific behavior may vary in accord with age, heredity, environment, experience and expectations about the disease.

Under the usual circumstance of an accidental discovery of a "lump" in the breast, a rather sudden sequence of emotional reactions and real life events is abruptly set in motion. These time periods in the patient's progress may be conveniently divided into (1) preoperative and (2) postoperative.

Preoperative Period

The zeal of cancer education in dispelling the shroud of ignorance has greatly enlightened the public, resulting in a subconscious alert to the common danger signals of breast

cancer No longer can most patients be deceived by innuendo or secrecy, the former handmaidens of fear and folly Perhaps a few patients may be indifferent or unaware of the warning signs while others may think there is some shame about cancer, yet a large number of women today are more or less aware that a "lump" in the breast requires prompt attention and further investigation

Anticipation and anxiety are perhaps the earliest emotional reactions which are aroused in the individual patient upon discovering a "lump" Acute anxiety may actually result in a serious delay in seeking medical attention However, if a physician is promptly consulted and operation advised then a series of evasive maneuvers may be the second stockade of defense against ultimate surgical therapy Nonetheless, many women are genuinely aware of the value of early diagnosis and early treatment and emotional adaptation is often made without serious psychologic resistance.

Yet the matter of delay (fig 48) in seeking treatment is a most important and disturbing problem to all concerned with the ultimate improvement of end results In a series of patients carefully studied by Shands, Finesinger, Cobb and Abrams (21) there appeared to be a discernible common denominator among the delinquents In answer to the question, "Why does a patient who knows she has a 'lump' in her breast delay in seeking treatment," one key to the query lies in the fact that "knowing" may occur on many intellectual levels The initial idea of "knowing" the relationship between a painless "lump" and the possibility of breast cancer may have alerted the patient, but the barricade may be in transforming insight into action Delay and delinquency may represent a psychologic process based upon anxiety

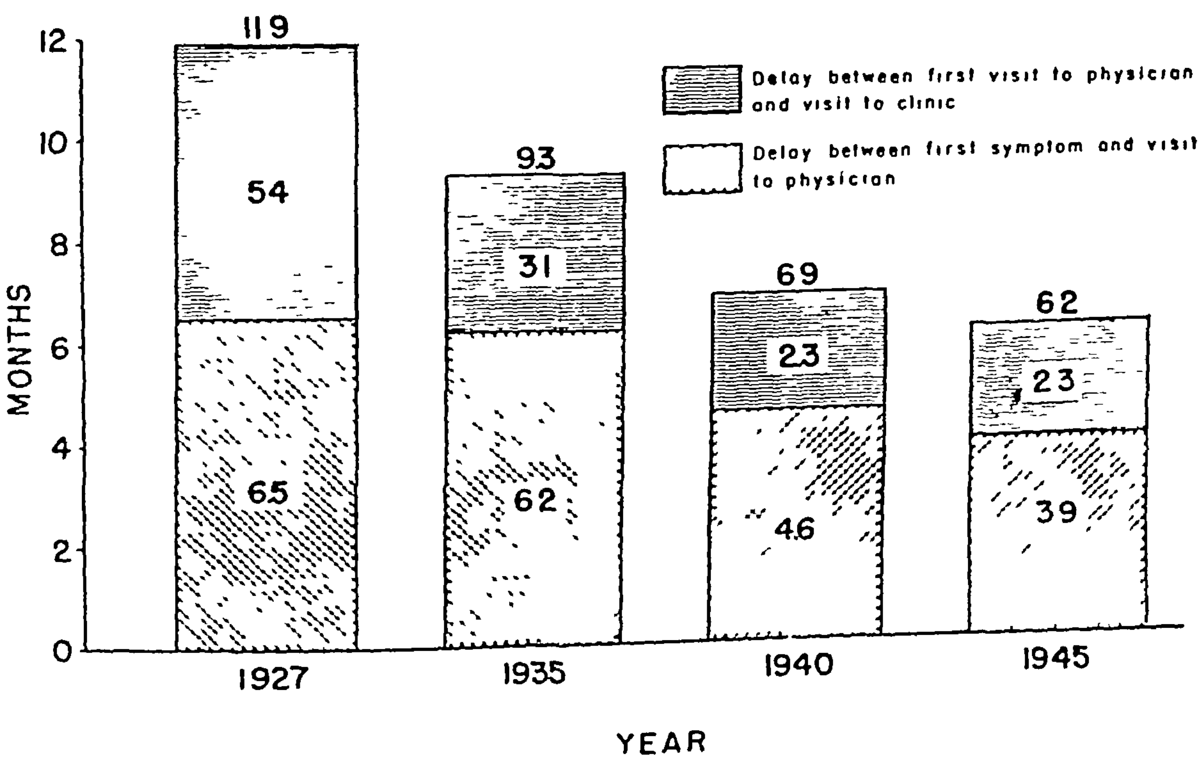

Fig 48 Delay of cancer patients in seeking treatment Massachusetts, 1927-1945 (Source Massachusetts Department of Public Health, 1948 Statistical Research Section, American Cancer Society, 9 48)

Instances of delay can be attributed to some defect in the mechanism of processing the information and knowledge which each patient already has in mind This interruption of thought may occur at any one of several levels and may be altered by mere happenstance Defensive maneuvers which patients often resort to are termed by Shands et al (1) avoidance where the patient overlooks the lesion (2) suppression, where the lesion is noticed and dismissed, and (3) denial where the significance is suspected but dismissed Psychiatrists have applied the term 'destiny neurosis' to patients who are well aware of the possibility of breast cancer but who react with the conviction that It is the will of God" Fatalistic resignation to the inevitable may make for a model patient yet this abject abdication to chance may also result in gross and aggravated procrastination

Delay in the diagnosis and treatment of cancer is a common failing and patients alone cannot be solely charged with personal negligence and full responsibility Pack and Gallo (16) have surveyed a large number of cancer cases among the general population and determined with whom the responsibility for the delay in diagnosis of cancer lay—the physician the patient or both A similar study undertaken ten years later by Robbins Conte, Leach and MacDonald (18) provides an excellent opportunity for comparing and evaluating the effects of cancer education on the public An important over all improvement during this time is noticeable in the percentage of patients in whom there was no delay Responsibility for patient delay decreased from 44.3 per cent to 31.2 per cent whereas delay on the part of the physician alone actually increased and still remains a serious censure of professional laxity Haagensen (8) has called attention to a recent survey in which only one-third of a group of women who were

TABLE 11

Comparison of Improvement in Responsibility for Delay in Diagnosis of Lay Patients after an Interval of 10 to 25 years

Responsibility	1923–1928 (Pack and Gallo)	1948 (Robbins Conte Leach and MacDonald)
	Per cent	*Per cent*
Patient	44 3	31 2
Patient and physician	18 0	12 9
Physician alone	17 0	23 4
No delay	20 7	32 5

After Robbins MacDonald and Pack (19)

sent to a physician of their own choice for a "Complete Physical Examination" had their breasts examined at all

A recent survey by Miller and Pendergrass (20) of more than a thousand cases of cancer of the breast showed the following five-year survival rates patients reporting for treatment within two weeks after apparent onset, 57 per cent, patients reporting for treatment one year or longer after apparent onset, 29 per cent Thus even if delay is not as important a factor in prognosis as we might have expected let no physician seek to justify his indifference to cancer education ("early diagnosis and early treatment") on the grounds of biologic fatalism

The precipitating factor that finally brings the delinquent patient to the physician may be of some serious import or merely a matter of trivial insignificance Pain bleeding from the nipple or ulceration are occasionally late but infallible signs of urgency, whereas a casual comment at the office or by a neighbor a chance remark by a brassiere saleslady or a breast operation among friends or members of the family may send the patient scurrying to the doctor

At the initial interview with the physician the discussion of the chief complaint will often be a more or less obvious clue to the patient's emotional concern regarding breast

cancer A careful family history and present illness will frequently elaborate the extent of this anxiety An understanding and considerate discussion of this common problem will allow the patient to express her natural fears and will make for a closer patient-physician relationship Herein lies the important art of listening

Following a thorough physical examination and those X-ray or laboratory studies which seem indicated, the diagnostic possibilities are clearly and carefully presented to the patient in terms which are simple and plainly understood When the clinical diagnosis of cancer seems most likely, a preliminary discussion in general and hopeful terms may be helpful in disclosing the patient's views about cancer The presence of a member of her immediate family adds immeasurably to the patient's peace of mind and decreases the possibility of individual distortion or misunderstanding

It is the physician's duty to inspire faith and hopefulness even while clinically confirming the diagnosis of a "serious breast tumor " It often takes only a doctor with courage and confidence to make a majority At this stage of the examination the terms "tumor" or "nodule" are certainly to be preferred to "malignancy" or "cancer " In most cases of breast cancer a definite and absolute diagnosis prior to breast biopsy cannot *and must not* be made! Such a decree may cause needless anguish and despair For although there is no royal road to operation, the duress of intimidation should never serve as a sentence to surgery There must, of course, be some appreciation of the seriousness of the disease, otherwise difficulty may arise in consent for prompt hospitalization and treatment

With widespread knowledge of the warning signs of breast cancer, it is inevitable that some patients with a realistic approach to life will demand to know, "Do I have breast cancer?" Since absolute certainty is impossible without histologic proof except in obviously advanced cases, perfect professional tact lies in the simple truth, "One cannot be sure without a biopsy " *Those diagnoses that are made before their time are always dangerous!*

It is desirable to describe in accurate and ofttimes painstaking detail the projected program of treatment in any one of several eventualities If recommendation for the operative removal of a suspected "lump" is made, reassurance should be given making it perfectly clear that biopsy and microscopic examination will be performed before reaching a final diagnosis and determining the extent of operation required Mention might be made of the fact that at most hospitals two-thirds or more of all breast operations are performed for benign breast tumors which do not require removal or amputation of the breast However, at some time prior to the day of operation a discussion of operative procedures and possible mastectomy is advisable

It is of the utmost importance for the physician to understand that the fear of mastectomy in the minds of many women may be intimately related to the symbol of feminine pride Lost in the limbo of our earliest culture and civilization is the origin of the relationship between the breast and its intrinsic sexual significance However, the anxiety about amputation or the possible mutilation of mastectomy may give a woman the illusion of irretrievable disenchantment "If all the world were homely, disfiguration would be no monster " The breast also bears the badge of motherhood as an organ necessary for the nursing of her young If a woman is shorn of this uniquely feminine symbol she may imagine herself bereft of the virtue of motherhood and denied so cherished a role

Not infrequently, however, a physician is initially consulted by a patient who is cate-

orically inoperable—or has all of the signs and symptoms of an almost certain recurrent metastatic or advanced breast cancer Despite obvious stigmata of the late nature of the disease every effort must still be made to confirm the clinical diagnosis quickly Until then the doctor's discretion depends upon the things he doesn t say For as Osler (13) has wisely warned "Errors of judgment must occur in the practice of an art which consists largely of balancing probabilities" If cancer is corroborated a satisfactory approach to the psychologic problem of how much should a patient know can be made by transposing the burning question into a smoldering answer In such cases morale props are mandatory and in general it is good practice to tell these patients only as much as they ask to know A guarded diagnosis slowly revealed enables a patient to prepare herself for ill tidings while sustaining hope The patient often senses the truth far more accurately than we imagine and any attempt to cushion the shock will be well repaid by a grateful understanding Many patients avoid seeking an exact diagnosis although it is my impression that almost *all* patients are eventually aware of the nature of their disease even though the word cancer has never been spoken Each patient arrives at this conclusion in her own way and the mainstay provided by the physician at this point is confidence and kindness

Hospitalization

The day of admission to the hospital may mean many things to many patients. Those at the extremes of the emotional scale may find the stress of hospital admission overwhelming The awesome impersonal routine of entering a hospital is often a harrowing ordeal even for those of exceptional fortitude and with the vantage of past hospital experience Many manifestations of tension or even panic may occur during the preoperative period Eating patterns are frequently disturbed, weeping is common, and insomnia is a serious problem for both the patient and nurse During this strange period of initiation the kind attention of merely the physician s presence is a most heartwarming and compassionate amenity that heals the mind in anticipation of healing the body The ennui of prolonged delay between hospital admission and operation should be avoided Whenever possible operation should be performed within a few days of hospital admission

It is a rule in most hospitals that all surgical patients sign an operative permit at the time of admission Since a surgeon is legally responsible to obtain consent for a *specific operation* it is not only the ethics of accepted practice but an essential prerequisite to explain simply and without provoking undue apprehension the eventualities subsequent to biopsy and prior to undertaking definitive surgery Thus the possible consequences of professional misconduct and the medicolegal offense of trespass are avoided However in so doing the final diagnosis usually becomes obvious to most patients by inference alone in the immediate postoperative period Patients who are the least bit perceptive often find out the nature of their disease by this web of indirect circumstance

Postoperative Period

Regardless of one s individual stability the psychological impact of radical mastectomy is certain to be immediately shocking and serious The drastic loss of so significant an organ makes the harsh reality of this initial reaction difficult to assuage Even while the area of operation is still swathed in dressings it must be assumed that most postmastectomy patients cannot be deceived regarding their diagnosis and, moreover it is not advisable to try Truth tempered by modera

tion is a wise prescription for the physician

Early in convalescence stress should be placed when indicated on the fact that the complete or radical operation was required in an effort to eradicate every possible vestige of the disease This point in selected patients may need emphasis and re-emphasis repeated many times over Particular prominence should be given in these early discussions toward convincing the patient that her postoperative recovery will be prompt and without resulting serious disability Arm motion should be encouraged, which attests in the patient's mind to minimal permanent impairment I frequently find it desirable in younger patients to stress in detail the golf, swimming and tennis achievements of similar patients who have also undergone radical mastectomy The cosmetic defect subsequent to surgery often results in serious dejection despite the airy attitude which some patients may assume The fear of future pain, cosmetic disfiguration or subsequent surgery (skin grafting or removal of the opposite breast) is almost inevitable and requires careful and convincing assurance made doubly sure The physician should be as honest as possible with each patient, trying to have her accept her illness as a fact rather than as a catastrophe or merely as an unimportant incident By allowing the patient to arrive at her own conclusions and gauging the tempo of this personal adaptation, one may avoid the intemperance of too much information given to patients with too little understanding The physician's responsibility rests upon careful counsel and consolation.

The impact of radical mastectomy and its natural inference of breast cancer stirs up quite naturally an intense emotional reaction within the patient Cancer carries with it the constant threat of death associated with a lingering and painful illness This can have a violently disruptive effect upon a patient's personality All of us when well are characteristically oriented toward the future and our usual behavior is predicated upon a normal sequence of events These predictions rest upon the expectancy of a long life, and to most of us the concept of death is more or less remote However, the abrupt awareness of breast cancer causes a drastic change in all of these personal probabilities In order to deal realistically with this new and serious complication of life a patient must undertake a challenging number of mental adjustments For some patients this difficulty becomes an impossible ordeal, and they resort to a variety of compensatory mechanisms similar to those noted by Shands previously These consist of suppression—keeping the status quo by noting but ignoring the unpleasant reality, denial—disregarding obvious or suspicious signs of significance, dissociation—the imaginary splitting of one's personality into observer and patient, identification—charting the course of the present illness in terms of a similar operation having occurred to a friend or near relative, and several other well defined psychologic defense mechanisms It would be surprising indeed if the grim reality of breast cancer did not result in the individual reorientation and occasional flight from the disease Also, the risk of suicide is an ever-present possibility, and it is the physician's duty to guard against this hazard when incipient self-destruction seems evident

In a study of guilt reactions in patients with cancer, Abrams and Finesinger (1) found that 93 per cent of the patients appeared to have a need for finding a cause for their disease Some specific past event is often referred to as being responsible for their cancer ("I struck my breast while house-cleaning," "That was the breast that gave me trouble while nursing.") The exciting cause was either their fault, or it was someone else's fault, but in most patients

there was self blame Many of the members of the families of patients frequently had the same anxieties and misconceptions of guilt as did the patients There were instances in which near and dear relatives considered cancer unclean sinful or contagious and denied the patient their consolation love and affectionate care at a time when she needed it most It is essential to stress the fact to members of the immediate family that cancer carries no risk of contagion and therefore there is absolutely no danger of exposure to the disease if children are allowed to visit the patient or adults aid in her care. In some serious situations optimal adjustment and rehabilitation can best be obtained only by resorting to appropriate psychiatric consultation and therapy

In the close relationship between physician and patient there often develops a unique fast and firm attachment or dynamic dependency which is an entirely new and most important emotional bond in cases of cancer During times of well-being or normal health each of us has a more or less stable and constant set of relationships upon which we habitually depend However the occurrence of cancer seriously disrupts this system of everyday dependency It is a common experience for all doctors to find that certain patients form a vital dependency relationship with particular physicians The bulwark of this decisive dependency is often directly proportionate to the seriousness of the disease and frequently reaches its climax with cancer Radical mastectomy with its attendant expectations of 'cure' comes to be the prime concern of the patient and all of her hopes and faith are crystallized in her surgeon This attitude is commendable and is to be encouraged When not excessive this allegiance can be a measure of real character for both the physician and patient alike and a source of much mutual serenity It is the surgeon's responsibility to accept and direct the total care of these patients

The initiation of postoperative X ray therapy may be required while the patient is still in the hospital A disposition toward therapeutic cooperation is more easily obtained if there is a genuine understanding of the disease The quicksand of concealment demands the disguise of a never-ending deception which may have the unfortunate consequence of ultimately interfering with proper treatment The essence of the physician patient relationship is built upon the virtue of respect and confidence There must be no shadow of doubt cast upon this confidence "Trust not him that hath once broken faith In betraying the faith of sensible and well informed patients (albeit with the best of intentions) one may inadvertently force patients into the pitfall of resorting to charlatans and cancer quacks However patients with faith in their physician are seldom deceived by the empirics of these impostors

Firmness of faith is often considered the highway to health Osler (14) noted long ago that more people sought help at the shrine of Ste Anne in Quebec than at all the hospitals in the Dominion of Canada Since the beginning of this famed shrine of Ste Anne de Beaupré in 1658, more than 27 million pilgrims have sought supplication at this sanctuary The crusade to educate the public concerning the so-called danger signals of cancer has undoubtedly resulted in a widespread "cancer consciousness " This all out campaign for early diagnosis and early treatment may ultimately influence or determine the attitude of physicians toward patients with malignant disease

Fitts and Ravdin (5) seeking to learn what physicians tell their patients with cancer interviewed a selected group of 444 Philadelphia doctors by means of a questionnaire The results indicated that 70 per cent

of these physicians either never tell their patients that they have cancer or usually do not tell them Thirty per cent either always tell their patients or usually tell them that they have cancer

Of particular interest was the fact that 94 per cent of the dermatologists tell their patients the truth, whereas only 41 per cent of the surgeons tell their patients that they have cancer Many of the surgeons indicated that the final decision was often made by the referring physician In the case of breast cancer I believe that this deception is especially dangerous and may engender a deep distrust of the surgeon

Fitts and Ravdin themselves offer no answer to their perplexing problem Perhaps it is safer to listen and take heed than to give advice "Our own opinion, after several years of study concluding with this investigation, might be best summed up in the words of one of the internists who commented on the questionnaire as follows: 'Most patients and almost all people who have discussed this problem with me have expressed a hope that they would be told the truth Most families of patients, on the other hand, have actually asked that the patient not be told In theory I believe that we should tell all patients except when there are definite reasons for not doing so I think that those reasons need clarification I do not know which patients I might make feel worse by telling, and therefore, I do not know with confidence which patients to tell ' "

Rennecker and Cutler (17) indicated that all patients in a group of 50 women with breast cancer were aware of their condition regardless of what they were told by their physician These patients were relieved when the opportunity presented itself of discussing the problem of cancer with a doctor

A most illuminating survey by Kelly and Friesen (9) indicated that 89 out of 100 patients interviewed with cancer of various organs and 729 out of 740 patients over 45 years of age undergoing cancer detection examinations wanted to be told the truth regarding cancer

Under very special circumstances it may be advisable to parry the patient's questions about the nature of her operation rather than tell her the harsh truth However, a direct lie is rarely, if ever, excusable Some time during convalescence at least one responsible member of the family is usually brought into confidence concerning the patient's condition The serious problem of breast cancer should be carefully but straightforwardly discussed with the family and the prospects for the future indicated in general but hopeful terms In a survival study by Lewison, Trimble and Griffith (11) at the Johns Hopkins Hospital it was found, as expected, that the prognosis of breast cancer is unpredictable Except for the extent of the disease in the regional nodes at the time of operation the histologic pattern of the tumor offered no basis for speculation whatsoever regarding survival It has been aptly said that whereas radical mastectomy may be a milestone in the life of a patient, it need not be a tombstone

The advantages of honest appraisal to the family can best be appreciated by sparing the surgeon the snag of consternation at an early recurrence on the one hand, or the entirely unexpected survival for a long period of time on the other If cancerphobia or anxiety is present in other members of the immediate family, it is wise to allay their fears by a personal examination

It is of considerable help in minimizing postmastectomy depression to enlist the intelligent cooperation of the husband During the duress of this trying period his attitude must be cheerful and reflect particular devotion and attention While

displaying endearment without pity or any evidence of rejection, he should emphasize the importance of the preservation of a happy family life

It is also desirable to interest the patient in brassieres and prosthetics during the early period of convalescence (see Chapter XIII) Another patient with a similar situation may be of decided help during this period of adjustment Group rehabilitation therapy has been highly successful in large hospitals. Many hospitals have specially trained nursing personnel who are accomplished and tactful in this intimate and time-consuming indoctrination Nurses working day by day with a patient as woman to woman are best fitted for this type of instruction and advice However, local or nationally known specialty stores, corsetieres department stores and surgical appliance and prosthetic stores have expert representatives who will visit hospital patients if necessary for this purpose Visual aids as well as a variety of prosthetics are available to assist in custom fitting and in creating the before and after' illusion During convalescence patients should be encouraged to use but not abuse their arm Routine arm exercises are especially valuable and hobbies which employ arm elevation are of special benefit

It is quite apparent that certain patients require a great deal more careful understanding than others but it is even more apparent that all patients need far more time and attention from their surgeon than they now receive Rehabilitation is a most important part of therapy Women want to know about their ability to resume their domestic activities drive a car, play golf wear a bathing suit lift the laundry or wear an evening dress They require the time consuming but all important reassurance of their surgeon—not their nurse not their neighbor not their near relative, but their surgeon—in a candid discussion of husband patient reaction future sex relationships, family planning and the problem of the "swollen arm" Regardless of a surgeon's skill in the operating room, he will be most esteemed by the patient for a deep sense of understanding during the postoperative period "Nothing is little to him that feels it with great sensibility"

The prospect of returning home is frequently viewed with a variety of emotional concern Most patients are eager to return to the intimacy of their home and have no misgivings about leaving the antiseptic atmosphere of the hospital However, other patients are afraid of the sudden threat of a hostile outside world with its social inacceptability and show added anxiety over disrupting the close dependency attachment which they have formed with their doctor The role of the family in restoring emotional equanimity and rehabilitation at this period of convalescence is of tremendous significance to every patient

Most minor postoperative complications (stitch abscess fluid beneath the skin flaps or delay in wound healing) are viewed by the patient with undue alarm as evidence of recurrent cancer' requiring further surgery Almost all postmastectomy patients are in constant fear of losing the remaining breast and often experience phantom pains and transient tumors. Such subjective symptoms require a liberal dose of physician reassurance and solicitude a kind of "digitalis for despair

There is very little known at present about the factors of host resistance to cancer but it certainly seems quite likely that the body mobilizes its defensive resources in an undisclosed manner Cancer cases of unusually prolonged survival rare instances of spontaneous regression and patients with exceptional periods of long term quiescence are most readily explained

in part at least, by inherent factors of increased host resistance It is often desirable that patients be made aware of this ally and potent potential force against cancer This may provide the patient with a spirit of conquest and personal participation against the disease, thus displacing the frustration of utter defenselessness

Psychologic Problems of Patients with Terminal Breast Cancer

The highest purpose of human endeavor lies in the compassion and consideration which we have for the suffering of mankind In all the mercies of the healing art there is no more compelling challenge to demonstrate the deft touch of the physician or the psychologic skill of the surgeon than giving comfort to those afflicted with incurable cancer It is in the relief of the dire distress of this ruthless disease that doctors distinguish themselves by the wisdom of their ministrations

General or local measures designed for the relief of pain are usually based upon practical palliatives, disciplined by experience and inspired by kindness Specific measures of alleviation such as supportive therapy, castration, hormone administration, radiotherapy, local treatment and the use of sedatives and narcotics have been appropriately discussed elsewhere in this book

The pessimistic philosophy of Sainsbury (20) is borne of despair, the convictions of a past era Today the disillusionment may still linger, but hormones and more effective radiotherapy and radioactive drugs give promise of effective palliation and a more hopeful future "To what end then this formidable array of remedies? To what end these general principles of application? To the relief of pain or of disease, generally, in the literal meaning of the word, to the greater efficiency of the body as a whole to the prolongation of life . Even then if we are able to relieve distress there is room for us, but if this may not be, if, on the contrary our efforts to eke out existence do but lengthen a hopeless struggle, fretting instead of bringing comfort, then it will be for us to remember that the obligation to protract life at any cost is not laid upon us if, thus armed, the futility of the strife is irresistibly borne in upon us, then we should put aside our remedia as cures, and ranging ourselves upon the side of Death, make easy the couch He would come as a friend, let us not compel him to hostility, since he must prevail ."

However, in dealing with the human equation of this terminal disease, physicians must inspire and preserve confidence while sustaining a full share of personal responsibility By precept and example the doctor often determines the human environment which affects the attitude of the nurse, the family and the patient herself This is particularly true in the face of difficult relatives A genial countenance is the essence of this encouragement Close attention and devotion to detailed directions as well as careful consideration to minor or major complaints makes for cheerfulness without mirth Gavey (7), in his prize essay on the management of the "hopeless" case, has stressed the importance of regular medical visits "It is not easy to visit 'hopeless' patients who have *insight into the gravity of the illness, but it is a fundamental* routine which the physician should not omit on the grounds that he can do no more and that the nurses have the treatment well in hand Gradually, imperceptibly, the physician can thus impart his knowledge that the patient's course is run, but never denying hope"

The relinquishing of final responsibility to the local doctor is an act of unkindness which selfishly serves as an evasive maneu-

ver on the part of the surgeon in-charge and which aggravates a heavy heart and renders worse the patient's oppression The full and final total care of the patient should remain the surgeon's responsibility Re strained and subtle sympathy should be specifically designed to give comfort to the patient's loved ones whose anguish and grief is often as great as that of the patient.

There is certainly no need to force the truth on those patients who show no desire to discuss their terminal illness Some patients are successful in personally ration alizing their problem while others are genuinely apathetic The physician's duty will vary quite obviously with the age of the patient, her fears and apprehensions, and the discipline of her emotional resources Treves (24) has summarized his own views 'Among the more painful experiences which haunt a doctor's memory are the occasions on which it has been necessary to tell a patient that his malady is fatal and that no measure of cure lies in the hands of man Rarely indeed has such an announcement to be bluntly made In the face of misfortune it is merciless to blot out hope The meager hope although it may be but a will-o the-wisp is still a glimmer of light in the gathering gloom Very often the message can be worded in so illusive a manner as to plant merely a germ of doubt in the mind which germ may slowly and almost painlessly grow into realisation of the truth'

Occasionally a woman insists on being told the truth She may wish to know her prognosis as nearly as possible so as to arrange for her family and personal affairs. Certain well-educated and enlightened women desire an exact diagnosis In the case of breast cancer their courage is furthered by the knowledge that medical science now has several strings to its bow—hormones, endocrine surgery radiotherapy and surgery

Life may be prolonged by the faithful adherence to a therapeutic regimen, and it often requires perseverance on the part of the patient and physician alike to muster courage to carry on However, the idea that something is being done on a rational basis offers encouragement to all

The religious needs of some patients are quite often their deepest needs It is a great glorification of religion that the choicest of blessings are frequently reserved for these last days With the spiritual support and invocation of the clergy, palliation of pain and dignity of distress mitigate much of the mental suffering Religion converts despair which destroys into resignation, which submits."

Whereas different religious beliefs and creeds are difficult to reconcile the physician is recognized as one without prejudice toward race, creed or color The distinguished Rhode Island physician and philosopher Elisha Bartlett is quoted by Osler (15) with these memorable words

Through their ministers and disciples they (physicians) have cheered the desponding they have lightened the load of human sorrow, they have dispelled or diminished the gloom of the sick-chamber they have plucked from the pillow of pain its thorns, and made the hard couch soft with the poppies of delicious rest they have let in the light of joy upon dark and desolate dwellings they have rekindled the lamp of hope in the bosom of despair finally when exhausted in all their other resources and baffled in all their skill handmaids of philosophy and religion they have blunted the arrows of death and rendered less rugged and precipitous the inevitable pathway to the tomb

Summary

Patients with breast cancer require support and understanding to meet the exigencies of so serious a situation Providing this warm-hearted inspiration is the responsibility of the physician- or surgeon-in-charge It is preferable that the operating surgeon, regardless of his own attitude toward cancer, assume full responsibility for *total care* The problem of anxiety concerning cancer should be treated individually in accord with the emotional status of each patient The needless abuse of over-explanation, obscurity, circumlocution and the quicksand of deception should be avoided It is advisable to assist each patient to arrive at her own rationalization or conclusions Counsel and consolation are a prime responsibility of the *surgeon* Generosity in bestowing praise for a patient's progress is a simple but most encouraging tonic Truth tempered by kindness may avoid the mistake of too much information being given to patients with too little understanding Active interest and careful follow-up should be regularly maintained by the surgeon throughout the full extent of the postoperative period By means of these compassionate considerations many patients will be spared the distress and suffering of unnecessary mental anguish

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CHAPTER VIII

Diagnosis

"It well repays the experienced surgeon to spend perhaps an hour in the examination of certain breasts The diagnosis has usually and unfortunately been exceedingly simple But women are now presenting themselves more promptly for examination, realizing that a cure of breast cancer is not only possible, but, if operated upon early, quite probable Hence, the surgeon is seeing smaller and still smaller tumors—cancers which give not one of the cardinal signs"

William Stewart Halsted, 1907

Introduction

Diagnosis is the procedure for reaching the most probable conclusion based upon the facts at hand The art of physical diagnosis is learned by faithful fulfillment of Osler's familar discipline (71) "Learn to see, learn to hear, learn to feel, learn to smell, and know that by practice alone you can become an expert" This precept of physical examination and diagnosis is particularly important to the general practitioner as well as to the internist and surgeon because, despite recent progress of modern medicine, many patients who seek preventive or routine medical care today are being given a cursory and inadequate breast examination Patients usually *consult their family* physician first Some of these busy general practitioners unfortunately are often forced for lack of time "to do by halves", thus missing an ideal opportunity for cancer control by *means of a careful breast examination* Cancer detection examinations in the past have even been looked upon with ridicule by some members of the profession

Haagensen (37) has called attention to the results of a recent public opinion survey in which it was "*revealed that in one-third of a* group of women who were sent to physicians of their own choice to ask for a Complete Physical Examination the physician did not examine the breasts at all" It is a sad and not uncommon experience to find a patient recently examined "except for my breasts" who comes in vain seeking help for advanced *breast cancer Furthermore, the false sense of* security provided patients after a most cursory type of breast examination is all too often a treacherous sanctuary for the ill-advised

If cancer could be *detected while it is still* a nest of cells localized to the breast alone it could, of course, be completely cured. The success of physical diagnosis in detecting the earliest possible cancer of the breast is dependent upon the thoroughness and skill *of* the examination. A complete breast examination is an orderly and unhurried procedure requiring patience, *practice and experience* Skill in the technique *of* examination comes

in doing. The early discovery of breast cancer is mainly a matter of taking the necessary time and trouble. The ideal occasion to establish a genuine and sincere patient-physician rapport is at the start of the first examination. This essence of good medicine in times of tension and anxiety requires an understanding of the heart while administering to those of bodily affliction. The precious ingredients of comfort are provided by courage and counsel. Respect for the personality of the patient is an essential prerequisite in this intimate contact involving human relations.

History

A discussion of the technique of history taking is beyond the scope of this work. However, among the necessary components of a good history are discretion and diligence and a power of perception for discerning the salient facts within the family history, past history and present illness. Each line of thought is to be carefully followed. Leading questions should be avoided. The patient's own words are particularly desirable in the *chief complaint*.

Although our accumulated knowledge of breast cancer is formidable, we have by far the greater part of its conquest yet to attain. Within the family history, past history and present history of each patient there may lie a rich reservoir of information. Diagnostic conclusions are often drawn from the many small particulars accumulated from within this reservoir. Also, the accurate analysis of important antecedent factors in the personal history of patients with breast cancer may perhaps disclose valid precedents for cancer prevention. Though still hidden in obscurity, the possibility exists that from among the embers of the past there may arise the hope and promise of the future. Through the combination of human cancer data plus experimental research and correlated biological studies, we may ultimately achieve this goal.

Many varied conditions in the patient's history have been incriminated at one time or another as being intimately related to the cause of breast cancer. Such contributing factors as age, heredity, marital status, pelvic disease, lactation, trauma, infertility, menstrual activity, endocrine abnormalities and the presence of previous benign breast disease (see Chapter VI) have all been presumed to be in some degree linked to the etiology of breast cancer. Discharge from the nipple is also an occurrence in the patient's history to be carefully investigated.

Many studies have been undertaken to ascertain the tangible influence of these past events in the destiny of patients developing both benign and malignant breast disease. The pattern for this type of investigation was set in England by the comprehensive work of Lane-Claypon (52) in her unexcelled study of breast cancer and its antecedent and associated conditions. Enriching the literature of this country are similarly excellent studies by Taylor (88) and Wainwright (89). A recent three-way comparison between patients with breast cancer, benign breast disease and a control series has been published by Lewison and Allen (55). This case-history and follow-up report consisted of three groups of patients studied at the Johns Hopkins Hospital:

1. 272 patients with benign breast disease.
2. 186 patients with breast cancer.
3. 107 patients without breast disease.

The control group was by no means normal but was selected from suitable hospital clinic patients otherwise picked at random.

Age

Cancer of the breast can occur at almost any age (see Chapter XIX) (rare cases have even been reported prior to puberty), although it is rather unusual to find cases after the age of 90 or before the age of 20. In a recent ten-city survey of cancer mor

Table 12

Resident Breast Cancer Cases Diagnosed in Philadelphia During 1948

Age	Number of Cases
Under 15	0
15–24	5
25–34	35
35–44	121
45–54	190
55–64	199
65–74	170
75 and over	102

bidity conducted by the National Cancer Institute of the United States Public Health Service (12), the figures shown in table 12 indicate the newly diagnosed breast cancer cases in a representative large American city during the year 1948 The incidence of breast cancer per 100,000 population increases progressively with each decade of age

The incidence of breast cancer and benign breast disease by age, in our experience, is recorded in table 13 In the benign breast disease group the average age for patients

Table 13

Age Period	Number of Patients	
	Breast cancer	Benign breast disease
15–19	0	18
20–24	1	27
25–29	1	36
30–34	4	44
35–39	12	[illegible]
40–44		
45–49		
50–54		
55–59		
60–64		
65–69		
70–74		
75 plus		
tients		
e		

with fibroadenoma was 30 years, with chronic cystic mastitis 42 years and with papilloma 47 years

The presence of a firm and solitary breast tumor discovered during the menopausal period of 50 must be regarded with a much higher index of suspicion than a similar lesion in a women of 25 Although 75 per cent of all cases of breast cancer occur in women past forty years of age, it is a serious mistake to regard all tumors in young women as benign Only one per cent of all breast cancer occurs in the male, yet there is a close similarity in the age incidence of the two sexes

Family History

The hereditary predisposition to cancer presents a problem that is most perplexing Whereas mammary cancer in mice has been clearly shown to be influenced by genetic susceptibility, hormonal stimulation and by the milk factor (see Chapter IV), the evidence for hereditary influence in humans remains to some extent vague and uncertain With a complete absence of plan in human breeding, any definite tendency toward the inheritance of cancer would be considerably attenuated Osler, in one of his waggish remarks, says that "varicose veins are the result of an improper selection of grandparents " However, *the case for cancer is not merely a matter of pedigree* Such complex factors as heredity and environment are both regarded as essential to the development of *human cancer*

The hereditary aspects of breast cancer have been carefully investigated experimentally by Maud Slye (83) and many others, and
nically by Lane-Claypon, Antoine and
on, Wainwright, Wassink
), Jacobsen (17), Smith
(75), Bush (10) and
e clinical studies
f a clear cut or
itary trans
o indicate

that cancer of the breast does have a specific hereditary tendency Breast cancer was found by Morse to be about three times as common in the mother of women with this disease as might be the expected incidence age for age, in the normal population Wassink found that breast cancer occurred with unusual frequency among relatives of patients having cancer of the breast and that the sisters of the patients were affected most often Jacobsen has published one of the most comprehensive investigations of the familial occurrence of breast cancer From his study he concludes that it is overwhelmingly probable that the development

TABLE 14

Family History of Cancer and Breast Cancer

Series	Total Number of Patients	Family History of Cancer		Family History of Breast Cancer	
		Number	Per cent	Number	Per cent
Breast cancer	186	47	25 3	17	9 1
Benign breast disease	272	60	22 1	15	5 5
Controls	107	15	14 0	2	1 9

of cancer of the breast is due to hereditary predisposition Smithers determined that a significantly high death rate from cancer of the breast occurred in the families of breast cancer patients Murphy (70) in an excellent monograph on uterine cancer published recently, also finds that the 'evidence supports the conclusion that hereditary factors affect the frequency with which cancer appears in the uterus.'

An excellent but as yet unpublished study of the biology of human breast cancer with particular emphasis on heredity is being carried out by Sheldon C Reed of the Dight Institute for Human Genetics at the University of Minnesota Conclusions thus far are in agreement with other workers that there exists a familial excess of breast cancer "However the data do not permit a conclusion as to whether or not genetic factors are primarily responsible for this excess" The observed number of cases of breast cancer among sisters of the propositae was almost twice the number expected by comparison with the sisters of the husbands There was no evidence for an excess of cancers other than breast cancer among the parents or siblings

The hereditary influence in our case study is clearly shown by the family history* recorded in the three series of patients investigated (table 14 and fig 49) A family history of breast cancer occurred in 9 1 per cent of the patients with breast cancer in 5 5 per cent of the patients with benign breast disease and in 1 9 per cent of the patients without breast disease Thus the incidence of breast cancer in the family of patients having this disease was almost five times as frequent as in the control patients The intermediate position in this series of the family history of cancer in patients with benign breast disease is in accord with current knowledge which indicates a small but firm core of common agreement (see Chapter VI) regarding the predisposition of patients with benign breast disease to breast cancer

However it is necessary to indicate the limitations of this type of data and to reemphasize the essential fact that the hereditary tendency to breast cancer is, to be sure, neither proved nor disproved by statistical surveys. It is quite obvious that only a few people have accurate information as to the precise cause of death of relatives who are more remote than their parents. Whereas there are women who are well aware of the exact cause of death of their grandparents

* The family history included parents grandparents and siblings Only the number of patients and not the number of cases in the family history were recorded

TABLE 12
Resident Breast Cancer Cases Diagnosed in Philadelphia During 1948

Age	Number of Cases
Under 15	0
15–24	5
25–34	35
35–44	121
45–54	190
55–64	199
65–74	170
75 and over	102

bidity conducted by the National Cancer Institute of the United States Public Health Service (12), the figures shown in table 12 indicate the newly diagnosed breast cancer cases in a representative large American city during the year 1948 The incidence of breast cancer per 100,000 population increases progressively with each decade of age

The incidence of breast cancer and benign breast disease by age, in our experience, is recorded in table 13 In the benign breast disease group the average age for patients

TABLE 13

Age Period	Number of Patients	
	Breast cancer	Benign breast disease
15–19	0	18
20–24	1	27
25–29	1	36
30–34	4	44
35–39	12	46
40–44	27	42
45–49	25	24
50–54	36	15
55–59	18	10
60–64	23	4
65–69	20	1
70–74	10	1
75 plus	9	4
Total patients	186	272
Average age	53 8	36.0

with fibroadenoma was 30 years, with chronic cystic mastitis 42 years and with papilloma 47 years

The presence of a firm and solitary breast tumor discovered during the menopausal period of 50 must be regarded with a much higher index of suspicion than a similar lesion in a women of 25 Although 75 per cent of all cases of breast cancer occur in women past forty years of age, it is a serious mistake to regard all tumors in young women as benign Only one per cent of all breast cancer occurs in the male, yet there is a close similarity in the age incidence of the two sexes

2. FAMILY HISTORY

The hereditary predisposition to cancer presents a problem that is most perplexing Whereas mammary cancer in mice has been clearly shown to be influenced by genetic susceptibility, hormonal stimulation and by the milk factor (see Chapter IV), the evidence for hereditary influence in humans remains to some extent vague and uncertain With a complete absence of plan in human breeding, any definite tendency toward the inheritance of cancer would be considerably attenuated Osler, in one of his waggish remarks, says that "varicose veins are the result of an improper selection of grandparents " However, the case for cancer is not merely a matter of pedigree Such complex factors as heredity and environment are both regarded as essential to the development of human cancer

The hereditary aspects of breast cancer have been carefully investigated experimentally by Maud Slye (83) and many others, and clinically by Lane-Claypon, Antoine and Pfab (7), Taylor, Wainwright, Wassink (91), Martynova (64), Jacobsen (47), Smithers (86), Penrose et al (75), Busk (10) and Morse (68) Although these clinical studies hardly support any concept of a clear-cut or well defined pattern of hereditary transmission of breast cancer, yet they do indicate

that cancer of the breast does have a specific hereditary tendency Breast cancer was found by Morse to be about three times as common in the mother of women with this disease as might be the expected incidence age for age in the normal population Wassink found that breast cancer occurred with unusual frequency among relatives of patients having cancer of the breast and that the sisters of the patients were affected most often Jacobsen has published one of the most comprehensive investigations of the familial occurrence of breast cancer From his study he concludes that it is "overwhelmingly probable that the development

TABLE 14

Family History of Cancer and Breast Cancer

Series	Total Number of Patients	Family History of Cancer		Family History of Breast Cancer	
		Number	Per cent	Number	Per cent
Breast cancer	186	47	25 3	17	9 1
Benign breast disease	272	60	22 1	15	5 5
Controls	107	15	14 0	2	1 9

of cancer of the breast is due to hereditary predisposition. Smithers determined that a significantly high death rate from cancer of the breast occurred in the families of breast cancer patients Murphy (70) in an excellent monograph on uterine cancer published recently, also finds that the "evidence supports the conclusion that hereditary factors affect the frequency with which cancer appears in the uterus

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The hereditary influence in our case study is clearly shown by the family history[a] recorded in the three series of patients investigated (table 14 and fig 49) A family history of breast cancer occurred in 9 1 per cent of the patients with breast cancer in 5.5 per cent of the patients with benign breast disease and in 1 9 per cent of the patients without breast disease Thus the incidence of breast cancer in the family of patients having this disease was almost five times as frequent as in the control patients The intermediate position in this series of the family history of cancer in patients with benign breast disease is in accord with current knowledge which indicates a small but firm core of common agreement (see Chapter VI) regarding the predisposition of patients with benign breast disease to breast cancer

However it is necessary to indicate the limitations of this type of data and to re-emphasize the essential fact that the hereditary tendency to breast cancer is, to be sure neither proved nor disproved by statistical surveys It is quite obvious that only a few people have accurate information as to the precise cause of death of relatives who are more remote than their parents. Whereas there are women who are well aware of the exact cause of death of their grandparents

[a] The family history included parents grandparents and siblings Only the number of patients and not the number of cases in the family history were recorded

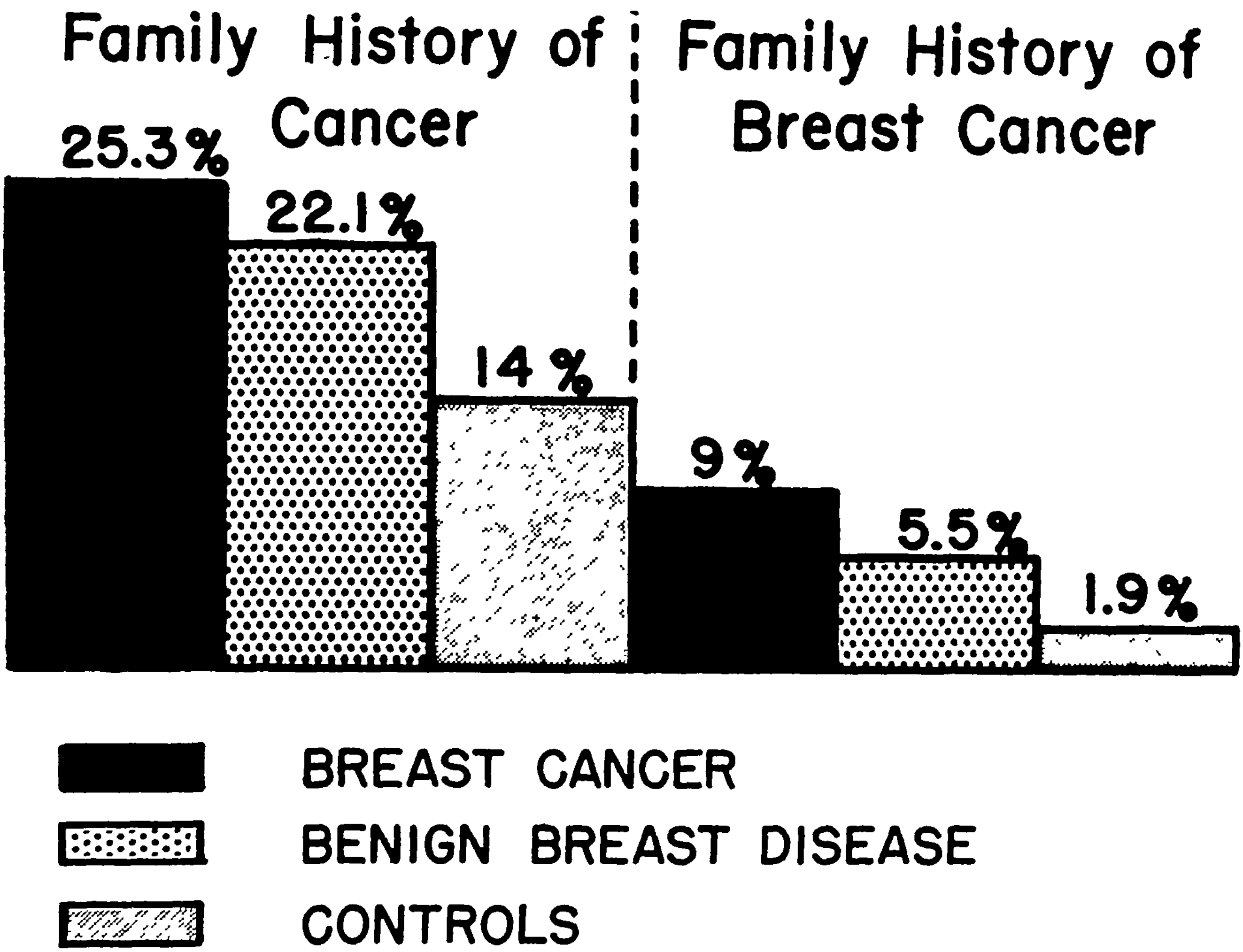

FIG 49 A positive family history of breast cancer occurred in nine per cent of the patients with breast cancer, in 5 5 per cent of the patients with benign breast disease, and 1 9 per cent of the patients without breast disease (controls)

this is by no means the rule Except for the memory lapse among older women there appeared to be no real difference in retentivity in the three series under study Moreover, it is of great importance to realize that the average age of patients with benign breast disease and patients without breast disease was well below that of patients with breast cancer Thus, conclusions concerning hereditary influence must be submitted to an unknown and variable correction factor due to this age differential before any assumptions can be considered valid However, if only the incidence of breast cancer in the family history of patients between the ages of 35 to 56 is considered in each of the three series, the influence of heredity gives the illusion of being actually enhanced The figures, however, are comparatively small and must be regarded with reservation (table 15)

TABLE 15

Family History of Breast Cancer in Patients of Age Range 35 to 56

Series	Number of Patients	Family History of Breast Cancer	
		Number	Per cent
Breast cancer	105	12	11 4
Benign breast disease	129	4	3 1
Controls	59	0	0 0

Mention should be made of one patient with breast cancer who had a family history of a maternal grandmother, mother, sister

and daughter all having had cancer of the breast Similar records of a kindred (Taylor citing Broca, Woolf and Gardner (97)) in whom cancer of one particular organ has run rampant, leaves one profoundly disturbed concerning the factors of inheritability in cancer

This review and discussion serves to emphasize the importance of the family history in the diagnosis of breast cancer Careful inquiry into the family history of cancer and in particular breast cancer must be made Among many other malignant diseases in which the role of heredity is suspect are the following cancer of the stomach esophagus and rectum, pelvic cancer neuroblastoma retinae glioma, leukemia lymphoma, neurofibromatosis, acoustic tumors and epitheliomata.

3 Gynecological History

The functional relationship between the breast and the female genital tract is clear and unmistakable (see Chapter III) Long ago Galen observed that cancerous tumors are found in all parts of the body, but particularly in the breasts of women after the cessation of menstruation which so long as it is regular preserves good health As early as 1825 Aitken suggested a possible connection between tumors of the breast and pelvic disease Actual morphologic changes in the breast are known to be quite closely related to the normal phases of the reproductive cycle Perhaps by reflecting the abnormality of pelvic disease or ovarian dysfunction the breast also might mirror the mischief of its misalliance.

In a gynecological survey of 100 women with both benign and malignant breast disease Pierce and Slaughter (76) noted that the incidence of pelvic disease 'was nearly four times that of well women of comparable age Cancer detection clinic figures were used in lieu of controls Demonstrable pelvic disorders of a significant type (not including inflammatory lesions or deterioration due to delivery) were found in 83 per cent of the patients. Twice as many cases of pelvic disease were noted in the patients with benign breast disease as in those patients with breast cancer Taylor on the other hand observed a previous history of gynecologic disease in only 42 per cent of patients with benign breast disease and in 32 per cent of patients with breast cancer

The gynecological history of all patients with breast tumors should be investigated as carefully as possible In considering the gynecological lesions in the personal history of patients all abnormalities requiring investigation or treatment of any kind either at the hospital or elsewhere, should be taken into consideration The results of our study are shown in table 16 The striking similarity between the controls and the patients with both benign and malignant breast disease was quite surprising because it not only conflicted with the cited conclusions of competent investigators, but it apparently repudiated any preconceived prejudices There was however an astonishingly high overall incidence of operative and nonoperative gynecological disease noted in our study of women with and without breast disease. This may have been due to the clinic material under investigation A careful history of gynecological abnormalities should include both organic and functional disorders

TABLE 16

History of Gynecological Disease

Series	Total Number of Patients	Gynecological Disease Number	Gynecological Disease Per cent	Gynecological Operations Number	Gynecological Operations Per cent
Breast cancer	186	93	50 0	54	29 0
Benign breast disease	272	170	62 5	79	29 0
Controls	107	64	59 8	33	30 8

4. Marital Status

As noted by both Dorn (23) and Gilliam (30), mortality statistics show a higher age-specific breast cancer rate for single women than for married women. However, since the marital status may not be maintained throughout one's entire life, the validity of cancer risk in single or married women based upon mortality rates alone may be open to considerable challenge. Authentic evidence can be acquired from case history studies which are especially designed to obtain specific epidemiological data both from cases and controls. Such studies are those of Lane-Claypon, Wainwright, Lombard and Potter (58) and Gilliam, all of which uniformly indicate that age for age in a large series of breast cancer cases there is apt to be a higher proportion of single women than observed in the controls or in the general population.

TABLE 17

Marital Status

	All Ages		Ages 35–56	
	Number	Per cent	Number	Per cent
Breast cancer				
Married	76	41	51	49
Widowed	63	34	22	21
Separated or divorced	34	18	25	24
Single	13	7	7	6.6
Total number of patients	186		105	
Benign breast disease				
Married	166	61	86	66
Widowed	24	9	16	12
Separated or divorced	42	15	22	18
Single	40	15	5	3.9
Total number of patients	272		129	
Controls				
Married	56	52	32	54
Widowed	28	26	17	29
Separated or divorced	13	13	8	14
Single	10	9	2	3.4
Total number of patients	107		59	

In view of this apparent prevalence of cancer of the breast among single women, it was interesting to compare the ever-married (married, widowed, separated or divorced) with the never-married (single) in the three series of patients comprising our Johns Hopkins Hospital study (table 17). Considering the average age differences between the three series, it was not surprising to find a high percentage of the never-married among the young women with benign breast disease.

However, if one considers the marital status of the three series only within the age range of 35 to 56, then the prevalence of single women in the cancer series becomes manifest. Despite the small number of cases in this study, the percentage of single women in this age-specific cancer series was 6.6 per cent, in the benign breast series it was 3.9 per cent, and in the control series it was 3.4 per cent. In a much larger series, Wainwright found the relationship of single women with breast cancer to controls to be 14.2 per cent to 5.9 per cent, a ratio somewhat more striking in proportion than the findings herein noted. It is indeed a double tragedy to find so many maiden ladies the victims of breast cancer. For in so serious a sickness their solitude seems even more remote and desolate.

5. Pregnancy History

In a comprehensive epidemiologic study of the marriage and pregnancy records of a group of several thousand patients, Gilliam found a significantly lower fertility rate among patients with cancer of the breast. Using a modified life-table technique which permits calculation of age-specific rates

TABLE 18

Fertility Rate

	Cancer Series Total Number 186		Benign Series Total Number 272		Control Series Total Number 107	
	Number	Per cent	Number	Per cent	Number	Per cent
Total number of women ever pregnant	128	69	163	60	90	84
Total number of pregnancies	430		509		474	
Total number of viable children	372	86	475	93	366	77
Total number of stillbirths and miscarriages	58	14	34	7	108	23
Average number of pregnancies per fertile woman	3 36		3 12		5 27	
Average number of children per woman having viable children	2 90		2 91		4 07	

based on a precisely defined period of risk Gilliam suggested that a reduced pregnancy rate may be related to cancer of the breast

A practical but less exact method of comparison is to simply record the average number of pregnancies in each of a series of cases and controls as tabulated in table 18

The relative fertility rate as shown in table 18 is in striking agreement with both the British figures (Lane-Claypon) and with the American figures (Wainwright) The average number of children per woman having viable children in the present study was 1 17 greater in the control series than in the cancer series The benign series was almost identical with the cancer series and this apparent reduced fertility rate was really not comparable because of the younger average of these women In the British analysis the corresponding figure for the average number of children per woman having viable children was 1.30 greater in the control series than in the cancer series and in the previous American analysis the difference was 1.8 greater The average number of pregnancies per fertile woman in the present study was 1 91 greater in the control series than in the cancer series Thus, it is quite obvious that the control series of women were distinctly more fertile than the women of the cancer series despite the fact that this later group were older and by virtue of age alone presented a longer period of pregnancy possibility The fertility rate as determined by the average number of pregnancies was 1 0 times greater in the control women than in the cancer women Although a reduced pregnancy rate may be related to breast cancer, all surgeons of experience have not infrequently operated upon women who have had exceedingly large families The role of excessive pregnancy with its consequent breast stimulation in the etiology of breast cancer remains to be defined

LACTATION HISTORY

If irritation and disruption of normal function are to be regarded as contributing factors in the etiology of cancer then it is desirable to examine the role of lactation in a study of breast cancer Adair and Bagg (3) reviewed the lactation history of 200 cases of breast cancer and found the incidence of abnormal lactation to be 91.5 per cent Breast stasis and ' inefficient drainage coincident with the formation of new mammary tissue were regarded as supporting evidence favoring the development of breast cancer More recently, Adair (1) indicated that at least one factor contributing to an

increase in breast cancer was the "growing habit of American women to not nurse their children" Lane-Claypon concluded that "any connection between cancer of the breast and lactation lies in the absence of function or in the excessive use of the breast" Taylor reviewed the role of breast stasis, abnormal involution, endocrine dysfunction and malformations of structure as possible contributing causes of breast cancer However, from a case history study of 155 cases of breast cancer and 116 cases of benign breast disease, he could find only a limited amount of evidence favoring the development of benign breast disease in women who were incapable of adequate lactation

MacDonald (63), in analyzing the functional activity of the breast in 2,636 cases of breast cancer, found abnormal lactation in 42 per cent of the parous patients Using Wainwright's figure that 20 per cent of normal women had lactation failure as a standard, MacDonald states that "failure of the breast to perform properly its physiological function is the most consistent apparent factor in the genesis of human mammary carcinoma" The decline of breast-feeding in America (present figures reveal only 50 per cent of infants are still being breast-fed at three months) has been a matter for critical comment in recent times Whether "abnormal lactation in 42 per cent of the parous patients" is actually excessive remains a matter of some speculation The general tenor of most contemporary reports is that mothers are increasingly unwilling to cooperate because of inconvenience or are frankly unable to cope with the physiological situation The effect of encouraging breast feeding on the premise that it promotes a healthier emotional relationship between mother and child is sound, but whether it may be of additional benefit as a prophylactic measure against breast cancer remains to be demonstrated

The lactation history in our study was reviewed from three specific points of view, (1) duration of lactation, (2) failure of lactation and (3) control of lactation The duration of lactation is recorded in table 19 by plotting the position of the child in the family against the length of time of breast feeding in the three series under study. Information was available for 372 viable children in the cancer series, for 475 viable children in the benign series, and for 329 viable children in the control series There appeared to be no significant difference between the white and negro races The most striking contrast was noted in those children recorded as not having been breast fed. Whereas 18 5 per cent and 19 2 per cent of the children in the cancer and benign series were not breast fed, only 9 4 per cent of the controls were not breast fed However, this difference is less impressive when the figures for the first two time periods are combined Premature cessation of lactation (breast feeding of less than six months) produced no significant difference in the three series of women under study. The data for excessive and prolonged lactation (breast feeding of longer than two years) were essentially the same for all three groups

The sundry and divers reasons for lactation failure are recorded in table 20 A comparison indicates a much greater preference among the cancer and benign breast disease groups not to nurse their children than among the control group By far the largest group of women in all three series could give no reason for their lactation failure other than insufficient milk This category included those women whose milk was inadequate in quality as well as in quantity

The various methods employed in lactation control are recorded in table 21 Although the validity of these figures is only as reliable as the memory of the individual women interviewed, yet it is interesting

TABLE 19

Duration of Lactation

Duration of Lactation	Series	Position of Child in Family												
		1	2	3	4	5	6	7	8	9	10	11+	Total Number	Total Per cent
Not breast fed	Cancer	20	13	12	0	7	5	2	1	0	0	0	60	18.5
	Benign	35	14	19	6	7	3	1	2	0	0	0	87	19.2
	Control	2	6	3	3	3	3	3	3	1	2	2	31	9.4
2 weeks to 6 months	Cancer	10	12	6	6	4	1	2	1	0	0	0	51	13.6
	Benign	40	20	18	11	6	2	2	1	1	1	1	118	24.3
	Control	17	17	15	9	10	6	5	5	4	5	2	95	28.8
6 months to 1 year	Cancer	37	[illegible]	15	11	8	8	6	3	1	1	1	113	30.8
	Benign	30	31	10	14	10	0	8	7	5	5	4	151	31.5
	Control	14	10	0	9	0	7	6	4	1	1	4	74	22.5
1 year or more	Cancer	41	31	21	17	12	6	4	2	2	2	1	130	37.1
	Benign	41	30	15	14	0	4	4	2	1	1	1	119	26.0
	Control	29	23	18	16	15	10	5	4	6	2	1	129	30.2

TABLE 20

Lactation Failure

Reasons Given for Lactation Failure	Breast Cancer Number	Breast Cancer Per cent	Benign Breast Disease Number	Benign Breast Disease Per cent	Control Number	Control Per cent
Nursing not desired	29	32.9	41	20.2	14	13.1
Insufficient milk	38	43.1	67	47.8	59	55.0
Not able to nurse	5	5.6	10	7.1	0	—
Mother sick	2	2.3	7	5	6	5.5
Abscess (breast)	1	1.1	3	2.1	1	1
Mastitis	0		1	0.7	1	1
Sore nipples	4	4.6	0		6	5.5
Baby sick	2	2.3	7	5	17	15.8
Baby premature	1	1.1	4	2.9	1	1
Twins	6	6.6	0		2	2

to note that the augmentation of the normal expulsion mechanism by means of the breast pump was practiced in 25 per cent of women without breast disease but in only 8.7 per cent of women with subsequent breast cancer. Massage, on the other hand, with its associated irritation and trauma, was commonly practiced among the women with both benign and malignant breast disease, but infrequently practiced among the women without breast disease. Spontaneous involution, presumably the most normal type of lactation control, was most frequently found in the control series. In view of the age differential in the three series under study, the administration of hormones (a relatively

TABLE 21

Lactation Control

Series	Method of Control*					
	Spontaneous involution	Massage	Binder	Breast pump	Hormones	No record
Breast cancer						
Number	40	41	10	9	3	10
Per cent	38.8	39.8	9.7	8.7	2.9	
Benign breast disease						
Number	44	55	16	21	17	16
Per cent	28.7	35.8	10.4	13.7	11.1	
Controls						
Number	44	10	12	23	2	0
Per cent	48	11	13	25	2	

* More than one method of control was reported by some women

recent mode of lactation control) could not be critically evaluated It must be clearly recognized, however, that there are certain obvious sources of error inherent in the personal equation of this type of clinical investigation which are liable to affect the accuracy of the history

MENSTRUAL HISTORY

Since the breast is not a static organ but rather a dynamic one dependent upon the action of hormones, it would be expected as a satellite of the female reproductive system to respond as do other target organs These often show signs of functional disturbance (see Chapter III) A history of menstrual abnormalities, delayed menarche or infertility associated with breast disease may reflect an altered endocrine environment produced by functional changes of the pituitary, adrenals, ovary, thyroid and possibly the pancreas Nervous stimuli are also rather indefinitely involved in these physiologic mechanisms

It has been well established that the cyclic changes such as premenstrual discomfort and breast engorgement which normally occur within the breast can be closely correlated with the degree of ovarian activity Time has been suggested as the fourth dimension—the reaction of certain organs to an abnormal endocrine environment acting over a certain period of time The complex changes which contribute to the problem of sterility may also have a causal relationship to breast disease

The menstrual history should include a careful inquiry into the use of drugs, and particularly the use of hormones for menstrual irregularities Whereas the causal relationship may be merely coincidental, there are authentic instances of breast cancer developing during the course of prolonged estrogen administration for the relief of menopausal symptoms Many doubts remain regarding the clinical relationship between minimal therapeutic doses of the female sex hormone even given over a long period of time and breast cancer, yet the possibility of this sinister link in certain cases cannot be excluded

I vividly recall a young woman who came to the breast clinic saying that ever since her doctor had been giving her female sex

hormones her breast "cyst" had grown considerably. At operation the patient had an extensive carcinoma with axillary metastases, and her survival was less than one year. Reasoning from a single case is tempting but often fallacious. To paraphrase Osler there are incurable diseases in medicine, incorrigible vices among doctors and insoluble problems in patients.

The effect of estrogens in causing gynecomastia is well known. The structural similarity between digitalis and the steroid nucleus has recently led LeWinn (54) to report 14 cases of gynecomastia occurring during digitalis therapy. The possible estrogenic activity of digitalis or other similar drugs is an interesting speculation which is now receiving careful study.

Trauma

As mentioned by Moritz (98), the carcinogenic possibilities of injury or mechanical trauma "would probably have long since ceased to stimulate any significant amount of scientific interest were it not for the fact that so many claims for compensation are filed each year in which it is alleged that a tumor has been caused by a mechanical injury." In a disease as common as breast cancer, where the cause is unknown, the liability to incidental breast injury so frequent, and the jingle of unearned riches from compensation insurance an enticing possibility, it is not surprising that fortune hunters and honest patients as well, so often tend to attribute their tumors to some trifling or serious preceding trauma.

However, the influence of a single uncomplicated episode of trauma as a cause of breast cancer remains highly problematical and open to considerable doubt. Transient injury as a cause of malignancy has been discussed by many authors and disputed for many years. Among early publications the analysis of a large number of collected cases by Deaver and McFarland (20) showed that only 0.5 per cent of the patients had given a history of injury antedating the development of breast cancer. Williams (95), on the other hand, only a few years earlier noted that 25 per cent of 137 cases of breast cancer gave a history of trauma, and Coley (15) mentions 52 cases of breast cancer which gave a definite history of a single antecedent injury. McWilliams (62) actually noted trauma in the history of 65 per cent of the patients with cancer of the breast. However, more recent authorities such as Pack (72) and Stewart (87) have relegated the role of trauma in the etiology of breast cancer to one of minimal importance.

Although there is much experimental evidence to indicate a vigorous cellular response and proliferation following injury, there is very little convincing evidence to indicate that this normal process of tissue repair may be actually transformed into a cause of cancer. Perhaps on theoretic grounds alone, as noted by Moritz, "it would appear plausible that the basic stimulus responsible for cellular multiplication in the process of repair and regeneration might be similar to that which results in tumor formation." It is permissible perhaps to speculate whether normal cells at the site of injury might be so subjected to environmental (circulatory and mechanical) changes over a long enough period of time to acquire malignant growth characteristics. However, there is no positive evidence to favor the theory that mechanical injury can cause cancer in previously normal tissue in man. The influence of injury in a diseased or abnormal organ remains to be more clearly defined. Nevertheless, one must be extremely cautious in applying the results of animal experimentation to man.

Stewart calls attention to the fact that breast cancer is primarily a disease of the mammary ducts and perhaps the commonest

ry or "rupture" of these
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in the etiology of cancer "

Although it is quite true that patients operated upon for benign breast disease do have a higher than expected incidence of breast cancer (see Chapter VI), yet in only three out of seven patients in our series did cancer develop in the same breast which was previously operated upon Thus, the support of this contention is seriously vitiated Also, if local operation with its consequent rupture of the duct-acinar system is closely allied to the origin of breast cancer, one might expect to find frequent evidence of injury and scarring associated with breast cancer Trauma, as is well known, is more apt to cause sarcomatous changes than carcinomatous Yet neither of these "potential" post-traumatic malignancies occurs with any degree of frequency considering the appalling accident and injury rate from automobile accidents alone

According to the reports of the National Safety Council, almost ten million disabling accidental injuries occur annually in the United States alone Incidental personal injuries in the form of non-disabling bruises and minor forms of trauma must be a very much more commonplace occurrence in the lives of all but the very sedentary or bedridden Thus, it is readily apparent that in accord with the laws of chance alone some form of breast injury may be expected to be incurred at some time during the long latent period known to be present in the development of breast cancer However, as emphasized by Moritz, "the fact that such a sequence may be pure coincidence does not eliminate the possibility that trauma may in certain circumstances cause tumor " Nevertheless, this possibility appears remote and may not necessarily indicate a cause and effect relationship

Pack suggests that very few case histories will fulfill the prerequisite postulates representing a relationship between trauma and the origin of malignancy (primarily sarcoma) A careful and critical history in all such cases for medico-legal purposes is a most important part of the examination

1 The site of injury should be carefully designated and recorded in relation to the region of subsequent tumor development

2 Proof and extent of injury should be recorded However, there is no more reason to believe (except quantitatively) that a massive breast contusion is any more likely to produce microscopic mammary malignancy than a trifling trauma

3 The time interval between injury and onset of tumor should be compatible with known causal relationships

4. Pack quotes Ewing as stressing the importance of "the previous integrity of the wounded part." Any evidence of prior breast disease should be recorded in the history

The role of trauma in patients who subconsciously resort to an assignment of cause for their breast cancer has been discussed in Chapter VII dealing with the psychologic aspects of breast malignancy These are the women who, when informed of the presence of a breast tumor, usually recall sustaining an injury "while house-cleaning" or "while caring for the baby." For these patients "every why must have a wherefore "

However, it is quite possible that a minor injury to the normal breast might go unnoticed, whereas pain may be intensified even if minimal trauma is incurred over an area of breast disease Accidental injury often leads to the discovery of a pre-existing breast tumor Ewing used the term "traumatic determinism" to describe the predisposition of an organ with a latent tumor to undergo injury He further coined the truism that "traumas reveal more malignant tumors than they cause."

Thus, most experimental and statistical

evidence fails to support the proposition that a single injury can cause breast cancer although no valid evidence is at hand which indicates that a single injury is absolutely incapable of being the sole cause of breast cancer Knox (99) who has carefully studied the relationship between trauma and tumors, states that, "with the advance in our knowledge concerning the nature of cancer, and its natural history, it has become more and more clear that there is no reasonable evidence of any relationship between a single injury and the production of cancer"

The role of trauma as an exciting force in accentuation or aggravation of an existing breast tumor must be considered in the light of the unpredictable natural history of the disease itself Perhaps it is possible for a single serious injury to cause sufficient local damage to adversely influence the course of cancer However if trauma is to be held responsible for acceleration of tumor growth the proof of this must be clearly evident

Clinical evidence that a breast cancer has been made worse by a traumatic injury is frequently held to be a sufficient reason for claiming compensation Yet in the eyes of the law, tumor injury must also have resulted in premature disability or death If aggravation of an existing breast cancer is claimed there should be some objective evidence to indicate that the time and character of the changes responsible for death or advancement of metastatic disease resulted directly from the injury and were not a part of the natural history of breast cancer

Actually a traumatic injury to the breast may be regarded at times as beneficial in that the patient's attention is directed to the presence of an unsuspected tumor thereby alerting the patient and causing the institution of treatment at an earlier period of time. Also there is some experimental evidence to indicate that injury may cause a disturbance in tumor circulation which is as apt to be followed by a temporary cancer improvement as by cancer aggravation In most instances, however, trauma *cannot* be related to either the acceleration or the regression of breast cancer The natural history of the disease is such as to have alternating phases of growth and resting periods during the normal progressive course of malignant disease

A carefully taken history can be of immense value in elucidating a fundamental relationship (if one exists) between trauma and breast cancer However all statements made at the time of the initial history must be subject to critical analysis and rigorous scrutiny Truth and not expediency must be the basic consideration In medico-legal matters involving injury and breast cancer "judgment may be weak but prejudice strong" The fidelity of the history must, of course remain inviolate

Justice today as noted by the J.A M.A (100) is dependent to some extent upon medical testimony in about one-half of all cases brought to the appellate courts in the United States Every trial is an adversary procedure In all actions it is the truth that is desired Yet medicine is not an exact science and many problems remain yet to be answered It is quite apparent that neither court nor jury is in a position unaided, to resolve or intelligently evaluate cause and effect relationships in breast cancer The medical expert witness has the opportunity and privilege to aid the court and jury in arriving at the truth It is his duty to assist in the administration of justice to the best of his ability Perhaps it would be even more desirable if a panel of impartial cancer experts could be called upon in these cases, not to appear on the side of either adversary, but to testify as a friend of the court Basic agreement under these circumstances would then be more than likely among these specialists, and their conclusions would reflect uniformity and truth.

Hypertrophy of the male breast (see Chapter XX) has been reported by Greene

and Howard (33), and others, in which trauma appeared to be an important etiologic factor. Griswold (34) has pointed out that among paratroopers the constant flapping of the parachute harness against the chest wall has given rise to a type of traumatic mastitis. Cancer of the male breast, however, as a result of a single uncomplicated injury remains exceedingly rare. Madsen (63a) reported the case of a 43-year-old male member of the Norwegian resistance army who suffered a sharp thrust in the left breast from a Gestapo gun barrel. A small swelling developed and persisted while the soldier was in a German prison camp. Several years later the soldier underwent a radical mastectomy for breast cancer with axillary metastases. Five years after the armistice the patient developed skeletal metastases and died. Gynecomastia, occurring while a prisoner of war, complicated the relationship between trauma and cancer in this patient.

Nipple Discharge

Hippocrates was the first to mention the association between a bloody nipple discharge and breast cancer (see Chapter I). In evaluating the history of the present illness, the significance of this sign lies in the insignificance with which it is so often regarded. Today, modern medical vigilance and cancer control require careful attention and cytologic study of nipple discharge in diseases of the breast. Riddell (78), in a recent Hunterian Lecture, states that it is "wise to accept with humility that however experienced we are, we cannot differentiate with certainty on clinical grounds alone between nonmalignant and early malignant" breast lesions. Every shred of evidence within the history must be carefully appraised.

Recently, Lewison and Chambers (56) reviewed a ten-year total of 2,195 patients hospitalized at the Johns Hopkins Hospital for a great variety of diseases of the breast. One hundred and fourteen of these patients had discharge from the nipple—an incidence of 5.2 per cent. Included in this group were patients whose primary complaint was discharge from the nipple alone, as well as those patients whose nipple discharge was secondary to clinically evident benign or malignant breast disease, or perhaps incidental to hospitalization for a primary disease unrelated to the breast. At the time of initial examination, 74 per cent of these 114 patients had clinical evidence of breast disease determined by history and physical examination. However, 26 per cent of the patients had no physical sign other than discharge from the nipple. Thus, no evidence of breast tumor could be detected in about one-quarter of the cases. The duration of discharge in all patients ranged widely from three days to seven years.

In a report by Hinchey (43), of all breast cases seen in the tumor clinics of the Massachusetts General Hospital and the Boston Dispensary, 8.3 per cent of 1,051 patients had nipple discharge. Many of these cases were "out-patients" and the diagnosis could be confirmed by microscopic examination in only 78 per cent. In a review of 2,269 cases of mammary lesions treated in the Department of Surgery at the State University of Iowa Hospitals, Donnelly (22) found 9.6 per cent with discharge from the nipple. There were in this series of patients 217 females and two males. At the Johns Hopkins Hospital there was an almost identical ratio of 113 females and one male with nipple discharge. The age distribution of patients with discharge from the nipple is recorded in table 22.

The spectrum of secretion from the nipple can be of almost any color and consistency. Separate ducts within the same nipple and at the very same time may secrete several

types of discharge During the course of close clinical observation it is not uncommon to find a change in the character or color of the initial discharge from the nipple A study was made to determine whether there was any constancy or correlation between the type of nipple discharge and a specific lesion of the breast The results are summarized in table 23 Except perhaps for papilloma there would appear to be only a random relationship between the type of nipple discharge encountered and the underlying mastopathy However all cases of papilloma with nipple discharge had either a serosanguineous or serous secretion Breast cancer and benign breast disease were quite similar in the types of nipple discharge noted Thus it would appear that no one type of nipple discharge is specific for a particular breast lesion and conversely both cancer and benign breast disease can give rise to diverse types of nipple discharge

Gray and Wood (32) note in their study of both benign and malignant papilloma of the breast that a discharge from the nipple occurred in 77 per cent of their 227 cases In all of their papilloma cases the secretion was serous or serosanguineous In discussing the significance of a serohemorrhagic or hemorrhagic discharge from the nipple Adair (2) Judd (49) and Miller and Lewis (69) found about the same proportion of benign and malignant lesions responsible for the abnormal discharge

Among the types of nipple discharge found less commonly one notes the occasional occurrence of a whitish or milky secretion This white discharge from the nipple may be milk, pus desquamated epithelium or carcinoma cells A cytologic examination of the secretion should insure a reliable and ready differentiation (see Exfoliative Cytology page 199) Cheatle and Cutler (13) reported one example of a thick white discharge which consisted of carcinoma cells from a subareolar duct cancer

TABLE 22

Age Range of 114 Patients with Discharge from the Nipple

Age	Number of Patients
11–20	2
21–30	17
31–40	31
41–50	38
51–60	15
61–70	10
71–80	1

TABLE 23

Relation of Breast Disease to Type of Discharge from the Nipple

Type of Nipple Discharge	Chronic Cystic Mastitis and Fibroadenoma	Papilloma	Cancer	Total
Serosanguineous	21	25	8	54
Serous	24	2	7	33
Whitish (milky)	11	0	1	12
Watery	3	0	5	8
Miscellaneous	6	0	1	7

Among the miscellaneous types of nipple discharge (table 24), one may find a thick greenish discharge from the nipple This is usually the result of retained secretions following lactation which stagnate within dilated ducts As suggested by Geschickter (29) this inspissated or grumous discharge may become contaminated with *Bacillus pyocyaneus* thus accounting for its green color Also it may be due to disintegrating blood pigment

The careful observations of many investigators have shown that most cases of nipple discharge are caused by (1) chronic cystic mastitis and fibroadenoma (2) papilloma and (3) cancer Donnelly noted that chronic cystic mastitis was responsible for 25 per cent (55 cases) of nipple discharge in his

TABLE 24

Incidence of Various Types of Nipple Discharge

	Hinchey	Donnelly	Lewison and Chambers
Serosanguineous	36 (54%)	121 (55%)	54 (47.4%)
Serous	16 (22%)	47 (21%)	33 (28.9%)
Whitish (milky)	5 (7%)	13 (6%)	12 (9.9%)
Watery	2 (3%)		8 (7.0%)
Miscellaneous	8 (13%)	38 (17.3%)	7 (6.8%)

series, intraductal papilloma was responsible for 30 per cent (66 cases) and cancer, including Paget's disease, was responsible for the remaining 45 per cent (98 cases). Hinchey found that proliferative cystic disease and hormonal dysfunction caused 54 per cent (36 cases), intraductal papilloma 10.5 per cent (7 cases) and cancer, including Paget's disease, 36 per cent (24 cases) of discharge from the nipple. In limiting the study to the bleeding nipple alone, Campbell (11) recorded the source of discharge as cystic disease, 24 per cent (13 cases), papilloma, 36 per cent (19 cases), and cancer, 38 per cent (21 cases).

From an analysis of the data generally available, benign breast disease accounts for about 60 per cent of the cases of nipple discharge and malignant lesions for about 40 per cent. In our cases (table 25), benign lesions of the breast were the source of almost 80 per cent of the cases of nipple discharge, whereas malignant lesions were the source of only 20 per cent of these cases.

Spontaneous nipple discharge is usually a reliable sign of abnormality within the breast. Despite the difficulties of differential diagnosis, secretion from the nipple may betray an early and unsuspected breast cancer. In our experience, a breast tumor could not be definitely palpated in 25 per cent of the cases notwithstanding the positive history of nipple discharge. One-fifth of these women subsequently proved to have breast cancer. The technique of eliciting nipple discharge (fig. 50) will be described in the section on palpation.

TABLE 25

Lesions of the Breast Causing Nipple Discharge in 114 Patients

	Number		Per Cent	
Benign breast disease	92		80.7	
Chronic cystic mastitis		46		40.3
Chronic cystic mastitis with abscess and inflammation		6		5.3
Chronic cystic mastitis with galactocele		2		1.7
Fibroadenoma		11		9.7
Papilloma		27		23.7
Malignant breast disease	22		19.3	
Carcinoma		13		11.2
Paget's disease		9		8.1

PAIN

Anatomy and Physiology

The brilliant French surgeon, Leriche, has said that "physical pain is not the simple affair of an impulse traveling at a fixed rate along a nerve. It is the resultant of the conflict between a stimulus and the whole individual." Although difficult to define, the sensation of pain is always unpleasant and reaction to it may vary from race to race, individual to individual, and from time to time. John Hilton has referred to pain as a monitor, "a starting point for contemplation which should ever be present to the mind of the surgeon in reference to treat-

ment " However the purpose of pain is not primarily that of a protective mechanism and this is particularly true in the diagnosis of malignancy When pain is present in cancer of the breast it usually heralds tissue damage and parenchymatous disruption of a considerable degree.

The conduction of pain centrally from the breast involves a minimum of at least three neurons (1) primary receptor neuron (2) connector neuron and (3) central neuron The primary receptor neuron sensitive to pain is simply a naked nerve ending The axis-cylinder divides and loses first its medullary sheath then its neurilemma and finally the naked branches of the axis-cylinder ramify freely in the skin and breast parenchyma To produce pain a breast lesion must lie in close proximity to these naked nerve endings

The central journey of pain conduction has been picturesquely described by Atkins (8) 'The painful sensations picked up by the sensitive nerve-endings are flashed to the spinal cord, some of these impulses travel relatively slowly while others travel at express speed In the spinal cord there is an all-change at the synaptic junctions in the posterior horn and from here taking leave of their erstwhile travelling companions—touch, position sense and their small relations—the pain fibers cross the track in the bridge of the anterior commissure and travel up the main line or lateral spinothalamic tract to the thalamus' The autonomic nervous system is also involved in the conduction of pain The physical sensation of pain is finally modified by an interplay between the thalamus and the postcentral gyrus of the cerebral cortex

Pain perception can be started by physical chemical or mechanical stimuli Adrian (5) is of the opinion that the initiating incident in the sensation of pain is a sudden increase in permeability of the surface membrane of the naked nerve-ending He believes that this surface near the end of the axis-cylinder, is readily broken by mechanical distortion The most probable stimulus in evoking breast pain as observed clinically is this type of tension or mechanical disturbance

FIG 50 Technique of circumareolar palpation to elicit site and source of nipple discharge

Breast pain may be divided into (1) skin pain and (2) deep somatic or breast pain Deep somatic pain may arise in the breast or subjacent tissues and is usually felt at the site of primary stimulation Referred pain may occur at a site other than the breast but usually in tissues supplied by the same or adjacent neural segments It may occur with or without associated hyperalgesia and hyperesthesia

Clinical

The diagnostic significance of pain in the breast in the history of women with breast cancer may be entirely incidental or irrelevant to the malignant disease Many women

are normally aware of some premenstrual breast engorgement, pain and tenderness, and the distinction between this type of cyclic pain and tumor pain may be a difference difficult to determine However, to accept the false concept that breast cancer is always a painless disease is to err in the opposite direction Whereas patients must be taught never to neglect a lump in the breast merely because it is *painless*, doctors must be taught never to regard a lump in the breast as benign merely because it is *painful*

River and his colleagues (79) noted a painful lump as the chief complaint in 20 per cent of their clinic cases with breast cancer In 2 per cent of the cases pain alone was recorded as the initial symptom (without the patient's knowledge of a lump in the breast) and this was due to malignant involvement of adjacent structures In their series of 105 cases of breast cancer, 24 cases were found to have a painful lump, and 78 cases were found to have a painless lump The somewhat increased incidence of pain as a presenting symptom may be due to the frequency of late and hopeless cases noted in this particular series

However, in a carefully studied group of 112 private patients with less advanced lesions, Goode and Martin (30a) found that 56 per cent accidentally discovered a "painless lump" whereas 44 per cent noted pain, burning, tenderness, itching or ulceration in addition to a "lump "

In general, the type of distress described by patients with breast cancer, chronic cystic mastitis or fibroadenoma is essentially the same Premenstrual exacerbation of mastodynia may be a subjective symptom of prominence in either condition However, there is considerably less delay in the discovery of a breast tumor if pain is associated with the presence of a lump

The great adaptive power of the breast with its loose lipoid component is sufficiently elastic to allow for even excessive tumor growth without pain or tension Thus, a rapidly growing medullary breast cancer can attain considerable size and yet remain absolutely painless When pain is present, Atkins has postulated that the pain-producing mechanism is an intense fibroblastic activity which causes mechanical distortion of the naked nerve-endings This is often associated with rapid tumor growth Fibroblastic frenzy may be only one explanation of breast pain Certainly the vascular engorgement of malignancy is another In contradistinction to vascularity, tumor growth does not stimulate nerve growth

Exquisite pain may be experienced in certain cases of advanced breast cancer where there is erosion of the chest wall, invasion of the pectoral muscles or ulceration of the skin Direct encroachment upon large nerve trunks probably serves as the source of pain stimulation

Deaver and McFarland indicated that pain was the initial symptom of breast cancer in only 9 per cent of their cases Mastodynia associated with benign breast disease is considerably more common Certainly pain is much less common as the presenting complaint than the accidental discovery of a painless lump In the early stage of the disease breast cancer probably causes pain less frequently than almost any other lesion affecting the mammary gland This may be true of even large tumors Many of us, I am sure, have looked aghast at patients with a huge and even ulcerative breast cancer which was said to be presumably painless The plaintive history of the clinic patient all too often begins with this solecism, "But, Doctor, it didn't bother me none, so I didn't bother it "

Corry (17) has reported that in 204 patients with operable breast cancer more than half had pain The pain may be intermittent or constant The incidence of stabbing pain

appeared to be unrelated to the histologic appearance of the tumor The pain threshold in individual patients varies considerably and is of importance in evaluating the degree of this subjective complaint

Pain associated with breast cancer may be (1) local, (2) referred, or (3) regional resulting from distant metastases

1 Local pain is usually caused by involvement of the skin subcutaneous tissues breast parenchyma or encroachment upon adjacent structures.

2 Referred pain may be felt in the homolateral arm shoulder axilla, back or neck Involvement of the intercostohumeralis nerve the intercostal nerves or the descending branches of the cervical plexus may give rise to a rather wide distribution of referred pain It is especially important in determining operability to differentiate referred pain from the primary tumor and the pain of osseous metastases which it often simulates This is particularly true of the lower intercostal nerves which may refer pain to the area of the thoraco-lumbar spine

3 Regional pain is most often due to bone metastases It is particularly important to know that pain in the back neck, chest or legs may be due to osteolytic or osteoblastic metastases and that this pain may precede X ray evidence of metastatic disease by several months or more *Persistent low back or pelvic pain in patients with breast cancer must never be regarded with indifference* Pain indicates unrevealed metastases until proven otherwise Persistent and severe bone pain is considered one criterion of inoperability However I have recently observed a postoperative patient with severe back pain in whom the X ray report was osteoblastic metastasis Careful follow up investigation over a period of time revealed the presence of a vertebral bone island mistaken for a metastasis and low back pain caused by retroposition of the uterus Aspiration or incisional bone or bone marrow biopsy in accessible areas should be used for diagnostic confirmation Often this technique is unnecessary but, on occasions (if positive) it is of valuable assistance in the differential diagnosis of an equivocal osseous lesion

I have seen on more than one occasion a patient riddled with extensive osseous metastases (confirmed by post mortem examination) whose skeletal X rays were interpreted as 'normal' not more than a few days prior to death Low back pain has been the initial symptom of late breast cancer not infrequently in patients with an occult or silent primary tumor (see Latent Breast Cancer page 198) These patients are often treated for 'rheumatism or arthritis until X ray evidences of metastases make their appearance Pain in the chest or the sharp agonizing pains associated with pleurisy may be the ill omen of rib mediastinal or pleuropulmonary metastases Abdominal pain is usually the result of metastatic disease causing encroachment upon a hollow viscus Pain in the hepatic region is the result of biliary obstruction or rapidly distending tumor metastases in the liver

If pain were to occur early in the natural history of this disease patients would report to their physicians promptly and earlier diagnosis could be expected Should the diagnosis prove to be benign an ideal opportunity would thereby be afforded physicians to teach their patients the principles and technique of self-examination It is indeed remarkable however that in the natural history of primary breast cancer the murmuring of pain is so often mute Perhaps no evil without its compensation

Miscellaneous

Additional salient signs and symptoms to be recorded in the history include fatigue cough anorexia, weight loss dyspnea and

disability or swelling of the arm Marked loss of weight is relatively uncommon in breast cancer despite the frequency of this sign in cancer of other organs When weight loss does occur it is often associated with anorexia due to hepatic metastases These are usually evidence of advanced disease and are of importance only in determining the course of future therapy—surgical, X-ray or hormonal Several statistical surveys have indicated a high incidence of thyroid disease in women with breast cancer This relationship bears further study

Present Illness

Painless "Lump"

The presenting complaint in the vast majority of patients with breast cancer has been the accidental finding of a painless "lump" in the breast The discovery is almost always made by the patient herself while bathing, dressing or during self-examination

The discovery of a "lump" in the breast is unquestionably the earliest and most common complaint in the present illness In a study by Shimkin et al (82a), he noted that 97 per cent of the patients first detected their lump or other abnormality themselves Haagensen and Stout (37a) reviewed the presenting symptoms in their series and found that 92 per cent of the patients came to the hospital primarily because of breast signs or symptoms Of this group 89 per cent complained specifically of a breast "lump" In the remaining 11 per cent of the patients, pain, nipple discharge, enlargment of the breast and abnormality of the nipple constituted the predominant reasons for coming to the clinic Breast cancer was incidentally discovered during routine examination in 5 per cent of the patients

Eggers, de Cholnoky and Jessup (23a) recorded a tumor in 77 per cent as the first manifestation of breast cancer in their series (table 26)

In the history of many cases of breast cancer a careful distinction should be made between those "lumps" which have appeared suddenly or have had a rapid onset and those which have grown slowly over a long period of time The history of onset may be of prevailing influence when this single factor is considered in conjunction with other indices of prognostic significance

Physical Examination

The diagnosis, and often the detection, of an early asymptomatic breast cancer is dependent almost entirely upon a systematic and carefully conducted physical examination In the earliest discernible lesion the cardinal signs of cancer are absent or may be barely perceptible and then perhaps only to the patient herself Certain alert women have become increasingly conscious of even the most minimal changes in the consistency and appearance of their own breasts The discovery of a lump in the breast is made most often by the patient Klopp, Hoyle and Blades (51), in an illustrative case history of early breast cancer, report a patient who noted by self-examination the barest amount of breast thickening On examination seven tumor clinic specialists considered the

Table 26

	Tumor	Ulceration	Pain	Deformity	Bleeding	Discoloration	Cracked Nipple
Number	255	15	12	12	6	1	2
Per cent	77 3	5 4	4 3	4 3	2 1	0 4	0 8

The chief complaint was not recorded in 15 (5 4 per cent) of the cases

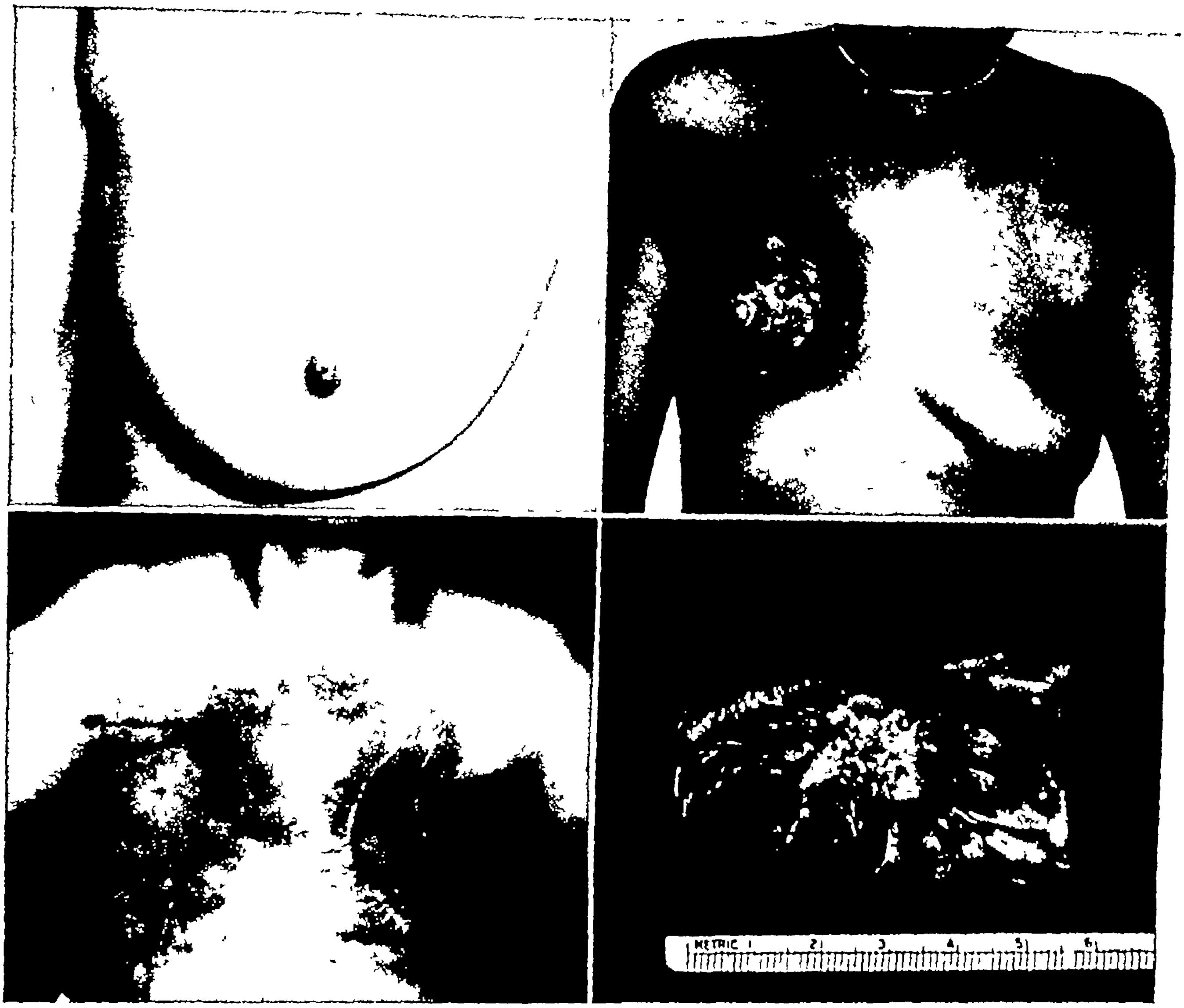

PLATE III

Upper left Early Paget's disease of the nipple

Upper right Progressive inflammatory carcinoma of the right breast treated unsuccessfully by X-ray and hormone therapy

Lower left Acute recurrent inflammatory carcinoma following bilateral radical mastectomy The skin became hard, brawny and thickened, characteristic of *cancer en cuirasse*

Lower right Infiltrating duct carcinoma with chalky streaks This type of tumor may be associated with extensive fibrosis causing the clinical signs so characteristic of retraction phenomena A F I P Neg Acc No 218758-C4 (Used with permission of F W Stewart, M D Tumors of the Breast, Armed Forces Institute of Pathology, 1950)

breast to be essentially normal Operation at the patient's request revealed an adenocarcinoma 3 mm in diameter

In order to detect the earliest subtle changes of breast cancer every examining physician must become thoroughly familiar with the normal appearance and consistency of the breast The female breast normally varies in size shape and consistency in accord with age development and previous pregnancy In the young adult the breast is usually hemispherical or cone-shaped and of a firm elastic consistency The borders are sharply defined and the entire breast is erect and tense but freely movable over the chest wall Later in life the breast may become larger and pendulous as a result of pregnancy and lactation The consistency of its parenchyma may vary considerably It may be smooth and soft granular 'shotty' or grossly irregular and nodular In both parous and nonparous women the breasts may become pendulous with advancing age but contour is mainly dependent upon adiposity At this stage the breast and its axillary tail is usually pear shaped

Inspection

Careful inspection is begun with the patient undressed to the waist and in a comfortable sitting position with her legs over the side of the examining table Awaiting the examiner to enter the room, feminine modesty is respected by having the patient drape a cloth cape over her shoulders This is removed when the examination is begun A good light is essential for inspection and the high lighting of retraction phenomena. A flexible gooseneck floor lamp has proven most satisfactory for this purpose

The size and symmetry of both breasts are carefully compared while the patient's arms are at her sides (fig 51A) and later elevated (fig 59) The round contour is inspected for flatness indentation protuberance or deformity The level, pigmentation and eversion of each nipple is noted Asymmetry in the size and development of the breasts is usually a constitutional variant which is considered quite within normal limits However, asymmetry as the result of a puckered and wizened breast of an advanced scirrhous cancer (figs 52 and 53) or the enlarged breast of a rapidly growing tumor or perhaps secondary to axillary lymphatic obstruction (fig 54A and B) are obvious signs of advanced disease.

The nipples and areolar areas are inspected for pigmentation erosion scaling retraction, flattening or tilting Evidence of recent nipple discharge may be apparent by the presence of nipple crusting Paget's disease often begins with an innocent appearing persistent crusting (color plate II opposite page 116 and color plate III A) Dilatation of the superficial veins (fig 55A) discoloration of the skin due to injury or the signs of acute inflammatory disease or inflammatory carcinoma (color plate III B and C) are inspection signs of major importance in differential diagnosis Inspection of the axilla may reveal the presence of aberrant breast tissue polymastia (supernumerary mammary glands present in the axillae) (fig 55B) lipomata, hidradenitis or tumor metastases.

Lymphedema of the Breast

One of the late but significant signs of breast cancer is lymphedema of the skin Swelling thickening and stretching of the skin occurs as the result of lymphedema The minute pores of the skin which are anchored by their deep-lying glands or follicles however cannot expand quite as readily Thus they form pin point dimples which give the skin the appearance of an orange peel This condition is commonly called 'pigskin' or 'peau d'orange' (figs 54B and 56)

Lymph stasis and transudation may result from mechanical obstruction to the normal

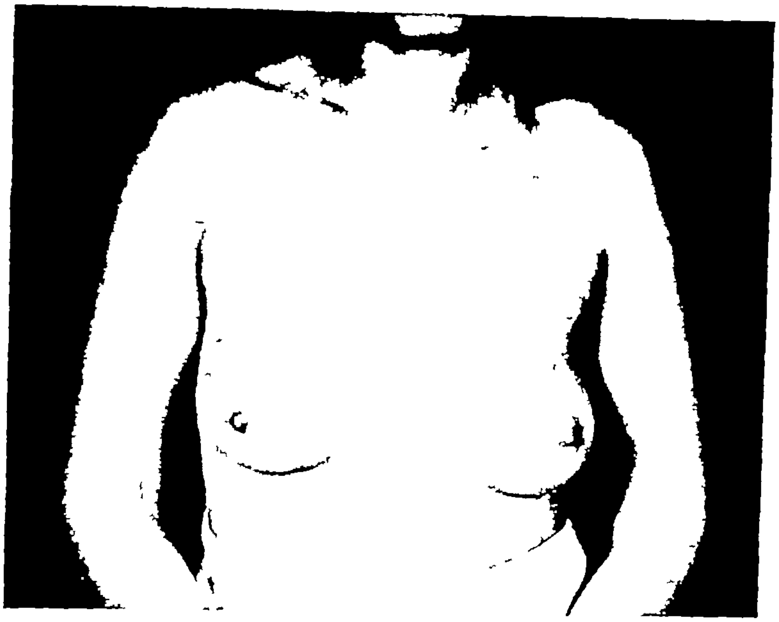

Fig 51A

Fig 51B

Figs 51A and B A Asymmetry frequently found in "normal" breasts B Protuberances and irregular contour in patient with extensive bilateral benign breast disease

lymphatic flow by the presence of an adjacent tumor-mass or by the plugging or obliteration of subdermal lymphatics A type of fibrosis of the stromal structures is evoked by cancer and this often involves the permeated lymphatics and surrounding tissue Handley's (41) important contribution to the study of cancer demonstrated the route of lymphatic spread of breast cancer by means of vertical branches communicating with the subdermal lymphatics A small area of thickening or actual edema will often be observed first in the region of the areola Deep-seated or occult breast cancers which have given rise perhaps to early axillary involvement may produce lymphedema or "pig-skin" of the most dependent part of the breast Elderly patients with cardiac decompensation and anasarca may also develop dependent edema of the breast

Lenticular nodules which appear as skin metastases can occur in the breast, axilla,

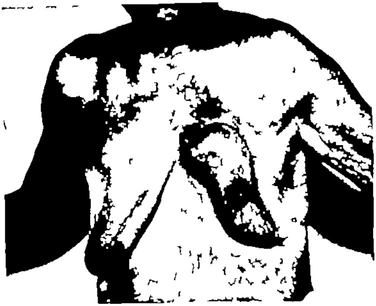

Fig 52

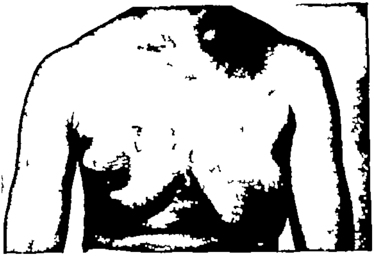

Fig 53

Figs 52 and 53 Marked retraction and puckering secondary to an advanced scirrhous carcinoma

neck, abdomen and back, and I have personally observed them as far afield as the wrist on the same side as the tumor These metastases may occur as an early evidence of advanced disease prior to operation or more frequently they may occur following mastectomy (fig 57A and B) The natural history of these nodules is slowly progressive although they may regress or remain stationary for long periods of time Their presence does not necessarily portend a poor prognosis Hormone therapy X ray therapy or surgical excision is frequently of considerable benefit and patients may survive in comfort for many months or years if given the advantage of energetic local therapy

The vertical branches of the skin lymphatics (Handley) are blind sacs which start in the tip of the papillae of the dermal layer of the skin and communicate with the dermal and subdermal lymphatic plexus. Cancer cells being carried along normally or

FIG 54A

FIGS 54A and B Marked enlargement of the breast associated with the local lymphedema characteristic of "late" lesions

FIG 54B

as retrograde lymphatic emboli (through devious collateral paths as a result of occlusion) may thus come to rest in one of these end sacs of the corpus papillare and give rise to a characteristic lenticular nodule Inspection of the skin should be carefully performed so as not to overlook these nodules or to confuse them when isolated with sebaceous cysts, fibromas or comedones

"Cancer en cuirasse" was the term applied

Fig 55A

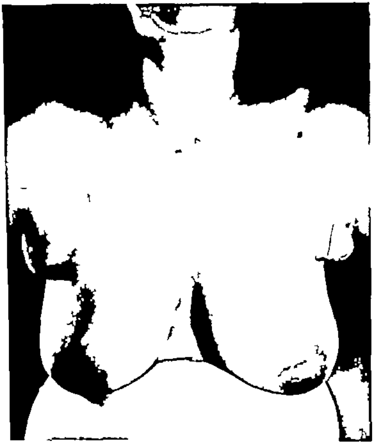

Fig 55B

Figs 55A and B A Infra red photograph showing the dilatation of the superficial veins on the left B Supernumerary breasts (polymastia) in both axillae

by Velpeau to the pachydermatous thickening of the skin associated with an unusual type of breast cancer It is characterized by a brawny hard rigid thickening of skin infiltrated by cancer The condition is considered to be a cancerous dissemination within the skin via the cutaneous and subcutaneous plexus of lymphatics associated with a

FIG 56 Pin-point dimpling of lymphedema which gives the skin the characteristic appearance of "pig-skin" or "peau d'orange"

FIG 57A

FIG 57B

FIGS 57A and B A Lenticular nodular local recurrences following radical mastectomy B Extensive nodular skin recurrences extending across the chest wall and in a retrograde manner down the arm

Fig 58 Postoperative cancer en cuirasse involving the contralateral breast

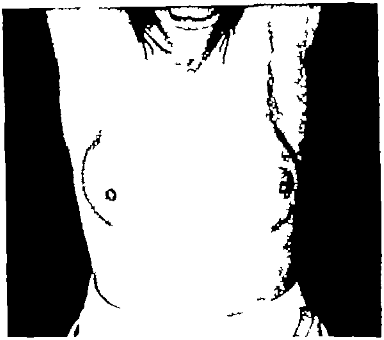

Fig 59 Apperance of normal breasts with arms elevated

brawny lymphedema (fig 58) Coalescence of the discrete lenticular nodules form a board like induration which girds the thorax and less often extends to the abdomen Discrete nodules identical with those seen in less extensive disease are present at the spreading margins of this distressing condition

Retraction Phenomena

While the patient is still sitting before the examiner she is asked to slowly elevate both arms above her head (fig 59) During this simple maneuver the breast is carefully inspected for accentuation of dimpling of the skin retraction or tilting of the nipple increase in the asymmetry of the breasts or obvious distortion of the normal breast contour (figs 60A and B and 61A and B) Several similar tests are designed to increase the prominence of retraction phenomena which are considered pathognomonic of breast cancer Fixation and signs of retraction are usually outward evidence of advanced disease and are due to fibrosis and scarring within the stroma which often accompanies epithelial neoplasia. Similar signs

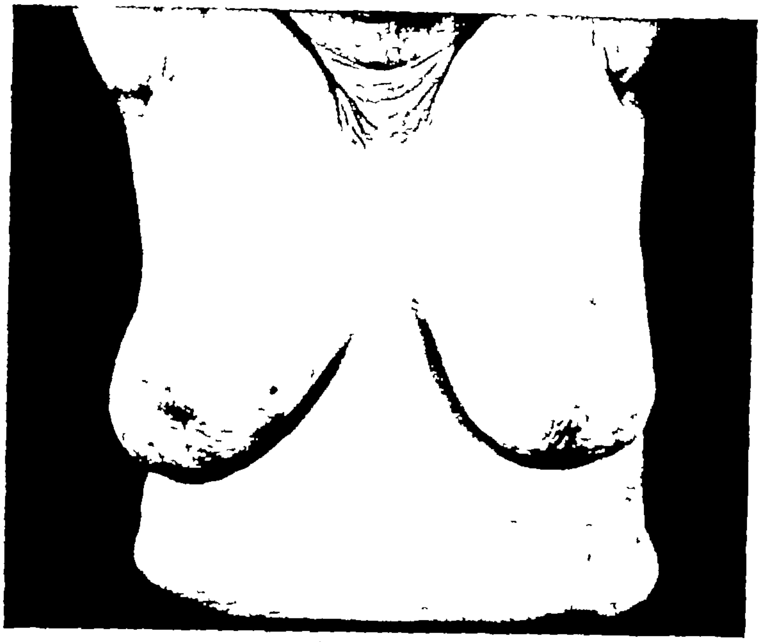

Fig 60A

Fig 60B

Figs 60A and B, and 61A and B Accentuation of the retraction phenomena of dimpling, nipple retraction and deformity of breast contour associated with elevation of the arms Despite the fact that the primary tumor in 61A (indicated by arrows) is a considerable distance from the nipple, marked retraction is evident

are occasionally noted in such benign conditions as fat necrosis, plasma cell mastitis, inflammatory diseases, hematoma associated with trauma and extensive scarring or fibrosis from almost any source

Malignant tumors in elderly patients may reach a considerable size without evidence of retraction (fig 62) These large cancers may appear to be encapsulated, surrounded by atrophic parenchyma and have a soft, rubbery consistency in place of the usual stony hard touch to palpation In contrast with this type of breast cancer, one occasionally finds a small deep tumor with marked retraction and breast atrophy A lobulated puffiness appears to be present quite superficially beneath the skin and may be mistaken for a lipoma

The forward bending exercise is another method of demonstrating the more subtle signs of retraction, particularly in the areolar region. The patient is requested to bend far

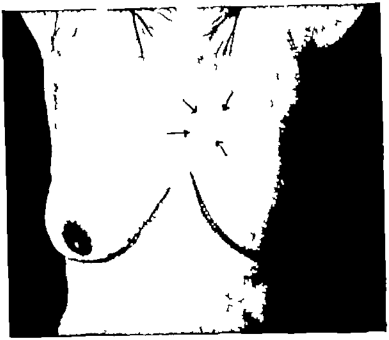

Fig 61A

Figs. 61A and B See legend on opposite page

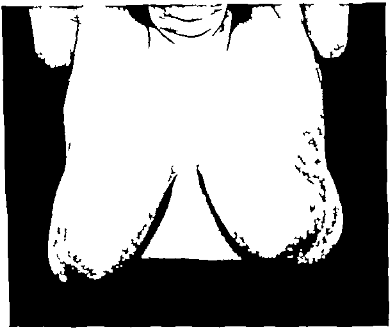

Fig 61B

forward with her arms outstretched in front of her where the examiner supports her hands In this way the breasts fall away from the thorax and hang freely from the chest wall The skin overlying a breast cancer will be abnormally fixed and bound down by fibrosis and diagnostic dimpling or asymmetry will be more readily detected (figs 63 and 64)

Contraction of the pectoral muscles is another very useful technique in demonstrating latent or manifest malignancy With the patient in the sitting position she is asked to rest her hands lightly on her hips (fig 65 A) The examiner then carefully inspects the contour of the breast for signs of retraction and compares the level and position of the nipples Next the patient is asked to firmly

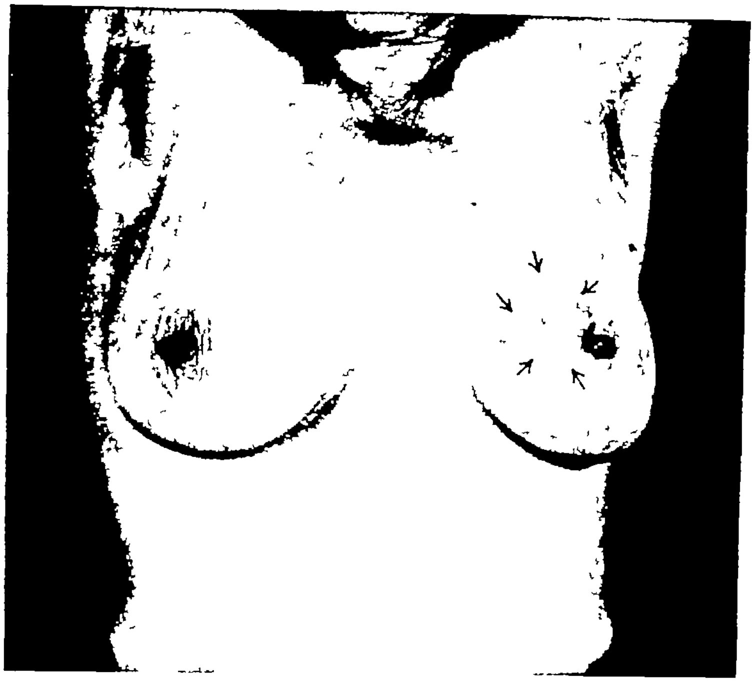

FIG 62 Large tumor of medial hemisphere of left breast showing evidence of skin invasion (indicated by arrows) Despite its location adjacent to the nipple, there is very little nipple retraction

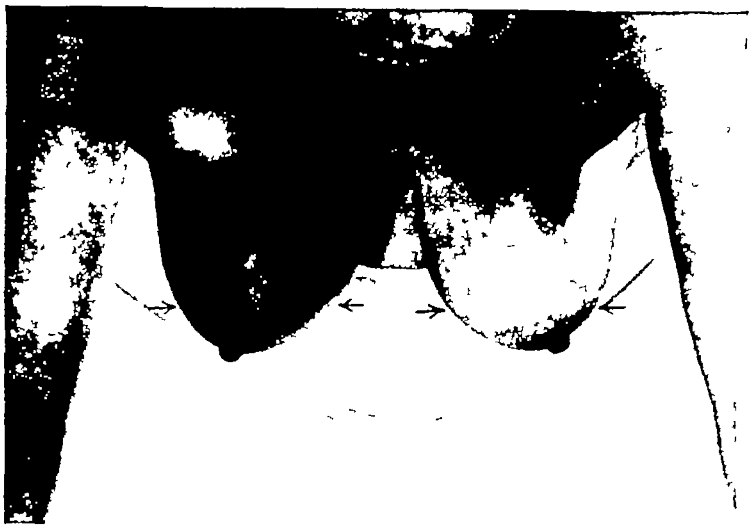

FIG 63 Forward bending maneuver revealing a very slight flattening and retraction of the left nipple A subtle difference in the rotund contour of the affected breast can also be noted in this "early" lesion These "early" signs are of the utmost importance

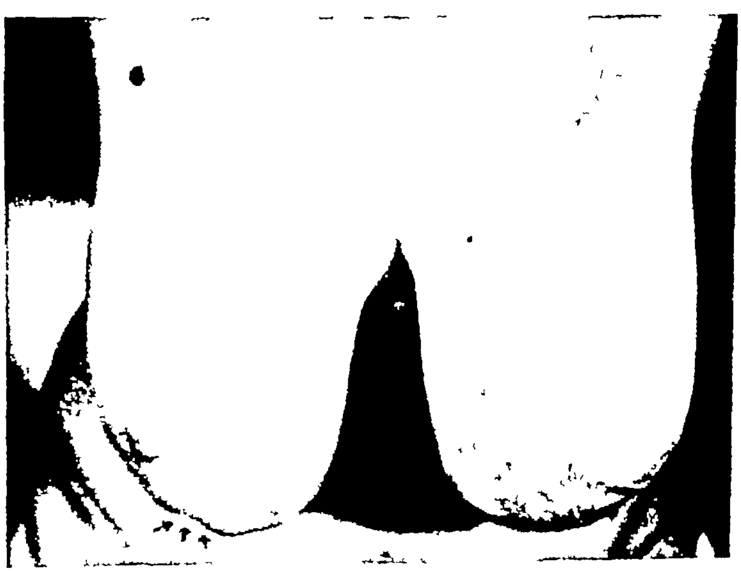

FIG 64 Forward bending maneuver showing a definite indentation (indicated by arrows) and change of contour of the right breast at the site of the tumor

FIGS 65A and B A Normal asymmetry with patient resting hands on her hips B Exaggerated retraction with arms firmly pressing hips

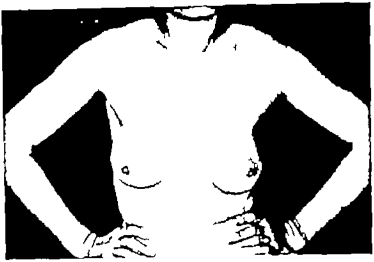

FIG 65A

FIG 65B

press both of her hands against her hips thus contracting the underlying pectoral muscles (fig 65B) Although both breasts may be slightly elevated by this procedure the tumor bearing breast will reveal an irregular area of dimpling geographical contour or elevation Careful inspection by means of a good light directed at the breast from several angles will usually accentuate these distinguishing nuances The prominence of this abnormality appears as the result of fibrosis and contracture within the surrounding stroma of the tumor bearing breast Fixation or attachment to the pectoral fascia causes an exaggerated contraction when the pectoral muscles are tensed (fig 65 B) In pendulous or fatty breasts this departure from normal may resemble the perspective of a relief map In addition to an overlying area of ridges and furrows the nipple may be deviated in the direction of the tumor A similar result may be obtained by having the patient lock her hands in front of her (by clasping the cupped fingers of one hand into the cupped fingers of the opposite hand) She is then told to pull against her hands and try to separate them Although the pectoral muscles are strongly contracted the examiner's vision is often obscured by the patient s arms thus reducing the clinical

FIG 66 Illustration of breast palpation from a late thirteenth century herbal.

value of this test from the examiner's point of view

Scarring and fibrosis following either a breast abscess or conservative breast surgery may distort the nipple or destroy the normal contour of the breast. By means of a careful history or the presence of a scar, this abnormality should be readily ascertained Involvement of the subareolar area by either a tumor, duct stasis or a chronic infection will result in nipple retraction or nipple flattening This must not be confused with nipple inversion (partial or complete, unilateral or bilateral) which is a common condition present for many years and entirely without clinical significance

It is well to be aware that in early breast cancer inspection may reveal no visible evidence of disease However, one must not be lulled into a false sense of security by this innocent inspection for wishful thinking is a dangerous substitute for experience Breast cancer will be found in direct proportion to the diligence of the search

PALPATION

Palpation of the breasts and regional nodes is first performed with the patient sitting up facing the examiner The supraclavicular and cervical regions are palpated gently with the tips of the fingers while the patient's arms are relaxed at her sides Supraclavicular nodes lying deep in the supraclavicular fossa or behind the sternoclavicular juncture can sometimes best be felt if the examiner stands behind the patient "Hunching-up" the shoulders may help the examiner The size, number, consistency and fixation of these nodes are signs of importance which should be determined Tumor-bearing nodes secondary to breast cancer are usually firm, fixed and low-lying in the supraclavicular fossa Clinically they are usually discrete rather than coalescent, but the lymphatic vessels may feel thickened and cord-like resembling a band of scar tissue

Palpation of the axilla is routinely performed as the next step Successful palpation

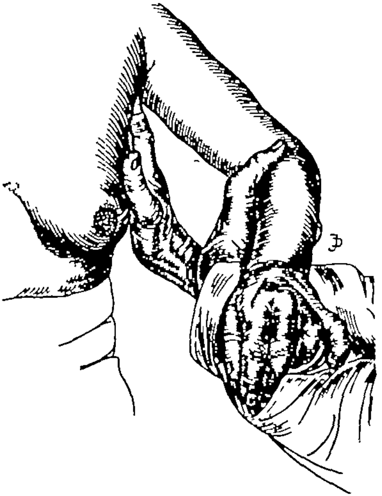

FIG 67 Method of examining the axilla Examiner supports the patient's forearm allowing complete muscular relaxation The correct technique of this examination is a most important part of physical diagnosis (Used with permission of Dunphy and Botsford *The Physical Examination of the Surgical Patient* and the publishers W B Saunders Co)

of the axilla depends upon complete relaxation of the pectoral musculature Manipulation must be gentle In examining the left axilla the examiner faces the sitting patient and supports the patient's left forearm on his left forearm while moving the arm passively from abduction to adduction (fig 67) With the fingers of the opposite hand the examiner reaches high in the relaxed axilla and palpates the nodes by partially cupping his hand and bringing his finger tips slowly down pressing against the chest wall This procedure should be repeated several times since small nodes lying either high in the axilla or behind the axillary border of the pectoralis major muscle may be readily missed In examining the right axilla the examiner supports the patient's right forearm on his right forearm and examines the axilla with the finger tips of his left hand The correct technique of this examination is a most important part of physical diagnosis

The number size consistency and mobility of the axillary nodes should be noted However palpation of the axilla is notoriously unreliable particularly in obese patients The very fact that the axillary nodes cannot be felt does not necessarily indicate their innocence The menace of the impalpable axillary node in physical examination is clearly shown in table 27 (modified after Westberg) (92)

Recently Riddell (78) in a study of 170 breast cancer patients noted that the axillary nodes were clinically palpable in 61 per cent however microscopic examination revealed axillary metastases in 79 per cent Axillary nodes were clinically impalpable in 39 per cent however microscopic examination revealed axillary metastases in 50

TABLE 27

The Error of Clinical Diagnosis in Palpation of the Axilla

Author	Year	Number of Patients	Positive Error*	Negative Error†
			per cent	per cent
Wevill	1932	98	16 3	36 7
Ahlbom	1934	400	28 0	22 5
Greenough and Taylor	1934	161	32 0	22 0
Harrington	1935	3381	32 0	29 0
Shore	1940	374	7 7	26 5
Roden	1944	311	13 3	26 8

* Axillary metastases clinically palpable but microscopically negative

† Axillary metastases clinically impalpable but microscopically positive

per cent Haagensen (36) has reported that 44 per cent of the Presbyterian Hospital patients had axillary metastases by microscopic study when the examiner had regarded the axilla as clinically innocent On the other hand, when the examiner had made a clinical diagnosis of axillary metastases, the axilla proved free of metastases in 15 per cent of the patients Perhaps these figures exaggerate to some extent the unreliability of axillary palpation in clinical diagnosis since it seems quite likely that in some cases metastatic axillary nodes might have been suspected without a definite diagnosis having been made

Axillary thickening or nodularity may be normally present in about one-third of all women In a personal survey by the author, of normal women examined during a cancer detection clinic survey, the axillary contents were found to be irregular and thickened on at least one side in 30 per cent of the group This physical finding usually represents axillary fat or areolar tissue, inflammatory enlargement of axillary nodes secondary to minor infections (residual or active) of the hands, arms or chest wall, or chronic hidradenitis of the axilla Neoplastic nodes are characteristically firm, fixed or stony-hard in consistency, usually discrete and rarely painful or tender

Palpation of the breast proper is next routinely performed while the patient is still in the sitting position Gentleness in palpation is a cardinal point in this procedure which should be both perceptive and precise Bimanual palpation of the dependent portion of a pendulous breast (particularly the subareolar region) can be most revealing (fig 68) On several occasions I have discovered by bimanual examination a small pea-sized, craggy, hard breast tumor beneath the nipple which easily escaped detection when palpation was performed with the patient in the supine position

Light palpation between the touch pads of the fingers of each hand is performed by a rocking motion, or moving the fingers up and down similar to piano playing Certain types of virginal, firmly fixed breasts, as well as certain portions of the breast itself (the upper quadrants), are almost impossible to examine by this bimanual technique

Palpation of the areolar area often reveals a wormlike mass of thickened ducts at their confluence beneath the base of the nipple Careful stripping of these ducts in a radial manner toward the nipple from several segments of the areola may give rise to latent nipple secretion Fingerpoint pressure clockwise around the areolar is a useful technique in localizing the source of nipple discharge (fig 69) Point pressure over a small nodule producing a serous or serosanguineous discharge may indicate the presence of a papilloma or cancer

In thin women with loose, pendulous breasts the subareolar region is readily compressible and by palpation has a cavernous or hollow feel Surrounding this subareolar area is a ledge of more substantial parenchyma which feels denser and is irregularly thickened Malignancies of this region are

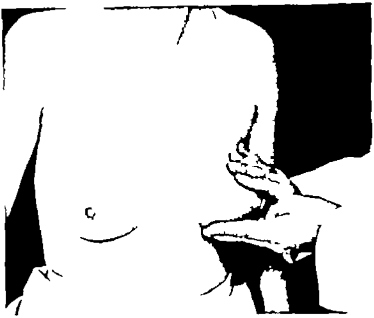

Fig 68 Bimanual palpation of the dependent portion of the breast Small tumors in the subareolar region can be most readily detected by bimanual examination

characterized by their firmness and fixation although calcified fibroadenomas and tense thick walled cysts with surrounding scar tissue can be most deceptive in differential diagnosis The doughy' feel characteristic of breast engorgement and hypertrophy during pregnancy may mask the presence of a small breast cancer

Many years ago Halsted (39) called attention to a rather uncommon diagnostic sign of gelatinous or colloid carcinoma of the breast When this type of cancer is superficially situated the tactile perception 'might be defined as a delicate swish or crush of a jelly like structure under tension, with the suggestion of a delicate bursting' This crunch of a colloid carcinoma may be the result of rather forceful and injudicious palpation

In elderly women with pendulous breasts who ordinarily do not wear a brassiere there may be present a certain amount of dependent edema which renders examination and diagnosis exceedingly difficult This is particularly true in women with clinical evidences of cardiac decompensation The thickened edematous pendulous portion of the breast is difficult to distinguish from a small tumor with associated lymphedema

Inspection palpation of the regional nodes and bimanual palpation in the sitting position being completed the patient is next asked to lie down It is occasionally advantageous to place a small pillow or pad beneath the shoulder to prevent the breast

Fig 69 Fingerpoint pressure clockwise around the areola is a useful technique for determining the presence of nipple secretion

on the side of examination from falling away laterally Most often, however, this can be accomplished by having the patient turn slightly or by supporting the breast on the chest wall between the thumb and index finger of the hand which is not being used in palpation

Inspection is again repeated in the supine position, first with the patient's arms at her sides (fig 70A) and later with each arm raised separately over her head (fig 70B) Palpation of the supraclavicular regions is performed while the patient is resting in the supine position (fig 71) It has been my experience that small or deep-lying nodes are most easily palpated when the neck muscles are completely relaxed by examining the patient lying down with her head on a small pillow Similar muscular relaxation is achieved in the supine position when reexamining the axilla using the arm resting technique described previously (fig 72) Complete flaccidity of the cervical and pectoral muscles reduces the risk of metastatic nodes being missed or overlooked. Previously impalpable nodes lying behind the anterior axillary fold may become quite obvious when the patient is examined lying down completely relaxed

Light and gentle palpation with the touch pads of the fingers of one hand is the most advantageous technique of examination The

FIG 70A

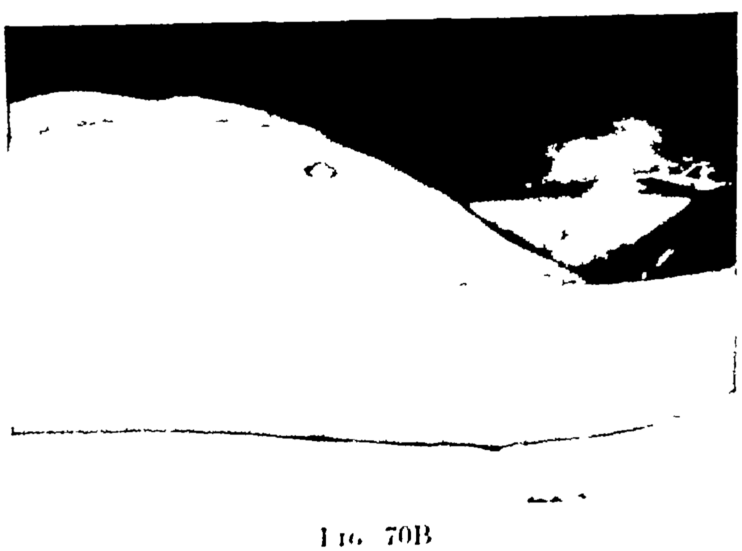

FIG 70B

FIGS 70A and B A Inspection in the supine position with patient's arms at her sides B Inspection in the supine position with patient's arm raised over her head

FIG 71 Palpation of the supra clavicular regions with the patient lying down

FIG 72 Palpation of the axilla using the arm resting technique de scribed

heavier the hand, the less will be the tactile perception A light rocking motion of the fingers is preferred to massage The entire breast is carefully palpated in an orderly and systematic manner first with the patient s arm at her side (fig. 73) and again with her arm raised over her head (fig 74) Each quadrant of the breast is examined in sequence In large pendulous breasts palpa tion may require the use of both hands but kneading or heavy massage is to be discouraged as needlessly traumatic

The periphery of breast tissue covers a large area and may extend from the clavicle to the costal margin and from the sternum to the latissimus dorsi muscle The axillary tail of the breast often extends high into the axilla and discrete or solitary tumors arising in this perimeter of the breast are often mistaken for more benign lesions However a tender, diffuse irregular shottiness of the axillary tail is a frequent finding in physical examination and is most often indicative of benign breast disease or premenstrual breast engorgement

Simply moving the breast gently from side to side first with the arm at the patient s side and again with the arm raised above her head will accentuate dimpling over an area of suspected tumor Even a very slight shortening of the fibrous trabeculae between the tumor and the skin will be accentuated by displacing the breast on the chest wall Merely an imperceptible tug or skin crease elicited by movement or dislocation of the breast in one direction only may be a highly

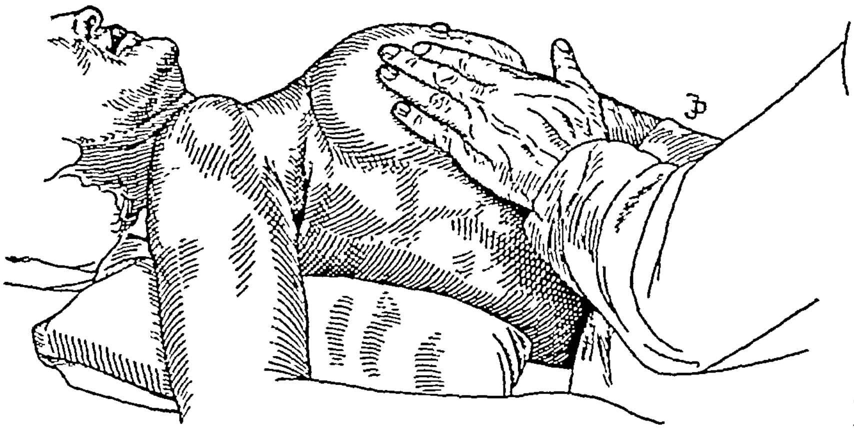

FIG 73

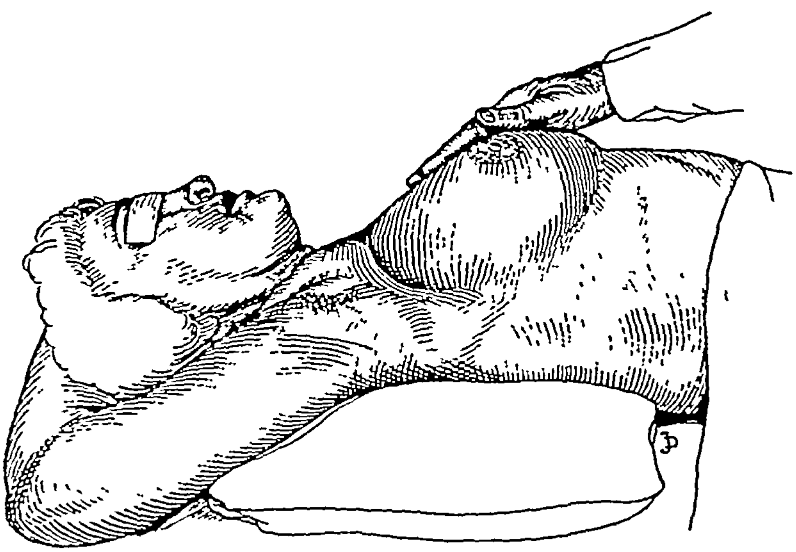

FIG 74

FIGS 73 and 74 The entire breast is carefully and gently palpated in a systematic manner, first with the patient's arm at her side and next with her arm raised over her head (Used with permission of Dunphy and Botsford, *The Physical Examination of the Surgical Patient*, and the publishers, W B Saunders Co)

rewarding diagnostic sign Specific tests designed to emphasize the telltale flattening or dimpling of the skin during this part of the examination have been variously called the "shadow test" by Scott (81) and the "plateau test" by Jackson (45) The so-called "plateau test" is performed with the flat of both hands placed on either side of the tumor Gently pressing the hands together normally produces a rounded mass of breast tissue between them In small tumors this can be done between the thumb and index finger (fig 75) In the presence of an underlying breast cancer, there is flattening of the skin with fine or coarse wrinkles hence the name "plateau"

The normal breast is composed of adipose tissue and glandular elements traversed and supported by strands of fibrous connective tissue The original description of these suspensory ligaments (fig 76) appeared in Sir Astley Cooper's book (16), "On the Anatomy of the Breast," published in 1840 He writes of these fascial strands

"The anterior or superficial layer passes upon the anterior or cutaneous surface of the breast, here it forms a fibrous covering, but not a true capsule, spread upon the surface of the gland, and passing between the gland and the skin, but it also enters the interior of the secretory structure Here it sends out two sets of processes of a fibrous nature from its two surfaces

"Anteriorly, large, strong and numerous fibrous or fascial processes, to the posterior surface of the skin which covers the breast,

into the substance of which it is received, and with which it is incorporated

'It is by these processes that the breast is suspended in its situation and I shall therefore call them the ligamenta suspensoria

Fibrosis and shortening of these suspensory ligaments which are so firmly connected with the skin contribute to the clinical signs of retraction and fixation so characteristic of cancer (fig 77) Merely lifting the breast away from the chest wall will reveal retraction and dimpling of the skin over the tumor area Deep-lying, small and presumably early tumors may not be as readily detected without these ancillary palpation procedures

In the event of discovering a single solitary or discrete tumor often referred to as a ' dominant lump the area should be reexamined to determine the tumor size consistency outline and fixation either to the overlying skin or underlying structures Fibroadenomas and lipomas have a characteristic slipperiness to palpation Carcinoma is hard—often stony hard craggy and fixed The characteristic tactile impression of elasticity in a small firm cyst under tension is difficult to determine despite the skill which comes of considerable experience A tense fluid filled tumor no larger than a pea exerts a certain pressure on the surrounding fibrous tissue and thus may appear to be by palpation much larger and harder than it really is These solitary cystic nodules are most deceptive in differential diagnosis

In the costo-mammary crease there occasionally occurs a small hard superficial tumor which is difficult to distinguish from a tense firm subacutely inflamed sebaceous cyst These very elusive cancers (fig 78A and B) are to be seriously regarded despite their innocent appearance and treated vigorously

However a small or even moderate-sized malignant tumor buried deep in breast tissue

FIG 75 Gently pressing the thumb and index finger together over the tumor produces a positive plateau test (Used with permission of Dunphy and Botsford *The Physical Examination of the Surgical Patient* and the publishers W B Saunders Co)

may be extremely elusive The admonition of Riddell— *Beware of the Ample Bosom* —is a wise forewarning based upon sound clinical experience The urgency to perform a breast biopsy is greatest in those patients in whom there is the greatest doubt in diagnosis For it is with these patients that the chance of cure is also greatest

The value of experience in physical examination lies not in seeing much but in seeing wisely

The following signs of significance are most important and should be carefully noted during the physical examination of the breast

A Location and size of tumor
B Is the lesion solitary or multiple diffuse or discrete?
C Character and consistency of lesion
D Presence or absence of tenderness
E Presence or absence of nipple discharge
F Evidence of lymphedema

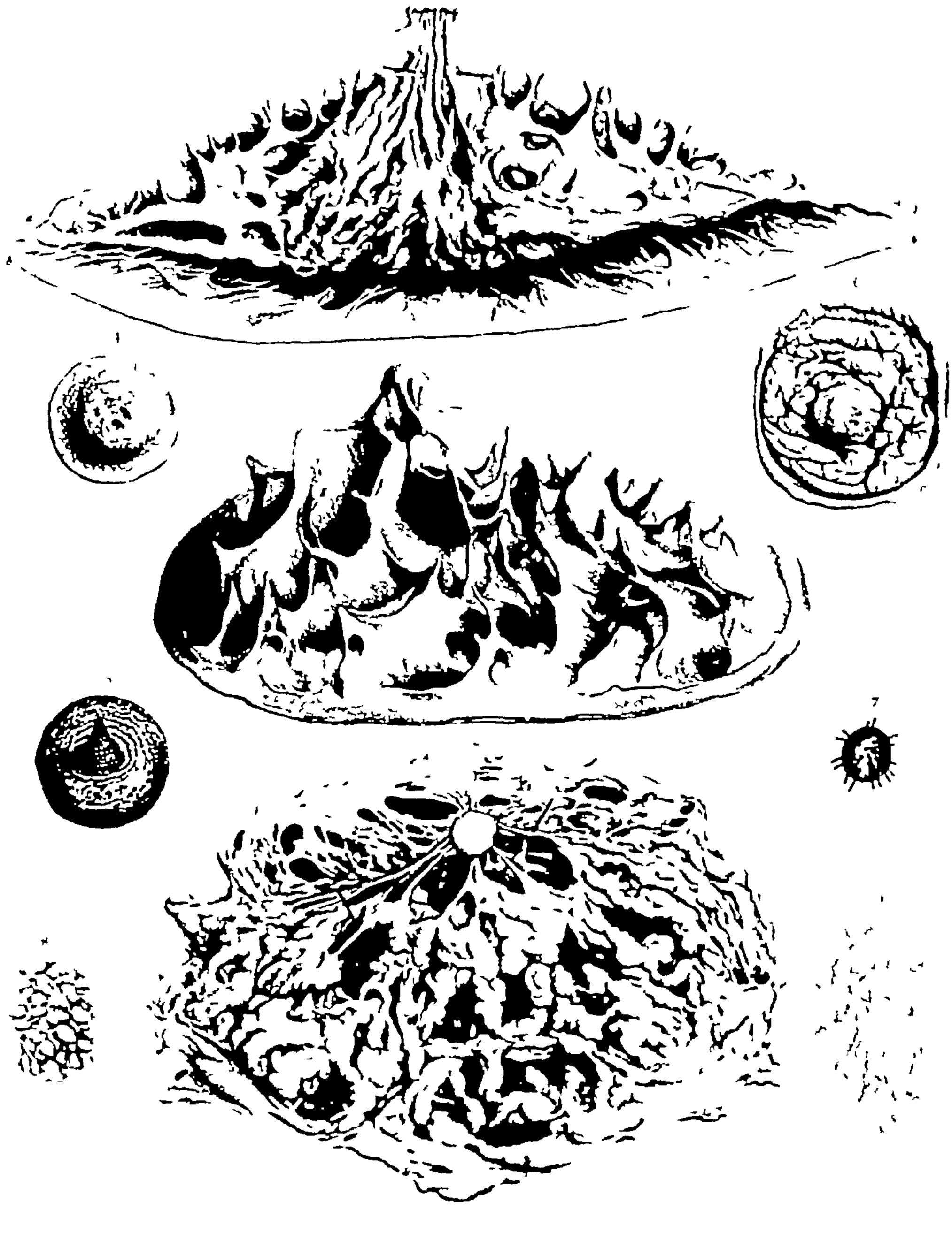

FIG 76 Original illustrations of the suspensory ligaments of the breast from Sir Astley Cooper's book, *On the Anatomy of the Breast*, published in 1840

G Signs of retraction or fixation to the
or underlying tissue

H Character and mobility of the reg.
nodes

All patients, in addition to receivin
thorough breast examination, are give
careful general physical ination wi
special emphasis on rdiova

evidence of remote
of the abdomen
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Differential Diagnosis

Cancer of the breast must be differentiated from benign breast disease, chronic and acute inflammations, the effects of trauma and sarcoma of the breast as well

Fibroadenoma

A firm smooth solid freely movable, round or lobulated painless tumor occurring in a teen age girl or young woman is most likely to be a fibroadenoma Beyond the age of 25 the diagnosis of this benign breast tumor is based more on probability than certainty and requires the refinements of a careful physical examination and biopsy for an unmistakable diagnosis These tumors are elastic well defined slow growing and encapsulated most often single but may be multiple and bilateral occasionally recurrent following surgical excision and rarely tender or sensitive to pressure In young Negro women it is not uncommon to find multiple fibroadenomas which are often bilateral An endocrine relationship between this abnormality of the breast and pelvic disease has been suggested

Fibroadenoma may simulate breast cancer particularly when it is calcified or when it is present in association with chronic cystic mastitis It is difficult indeed to differentiate a lump from a lumpy breast. When in doubt *biopsy is recommended as the safest measure*

Chronic Cystic Mastitis

It is a major problem in diagnosis to differentiate *an area of chronic cystic mastitis* which occurs so commonly in 'normal' women from an early or small cancer of the breast Although the average age of patients with this baffling benign disease is somewhat younger than patients with breast cancer there is a considerable age range of overlap Chronic cystic mastitis is usually a diffuse disease with bilateral areas of *nodularity* and shottiness Large or small cysts may be

Fig 77 Fibrosis and shortening of the suspensory ligaments of the breast giving rise to marked retraction of the nipple or dependent portion of the breast

present Signs of fixation and retraction are absent but there is often a disturbing degree of tenderness to pressure associated with a history of accentuation of premenstrual mastodynia Individual cysts if deep may be firm thick walled and tense giving the examiner the false tactile impression of a stony hard solid tumor A low grade chronic inflammation may cause these cystic areas within a region of chronic cystic mastitis to become adherent to the surrounding tissue and even cause skin or nipple retraction Under these circumstances (particularly if the lesion is deep-seated or located in the axillary tail of the breast) the differential diagnosis becomes exceedingly difficult Transillumination is of value only if the cysts contain clear and non turbid fluid Nipple discharge if present may be white or serous Nodularity of a firm consistency, diffuse or localized within the axillary tail of the breast, requires diagnosis by biopsy A favorable *prognosis rests upon the prudence of prompt* diagnostic excision

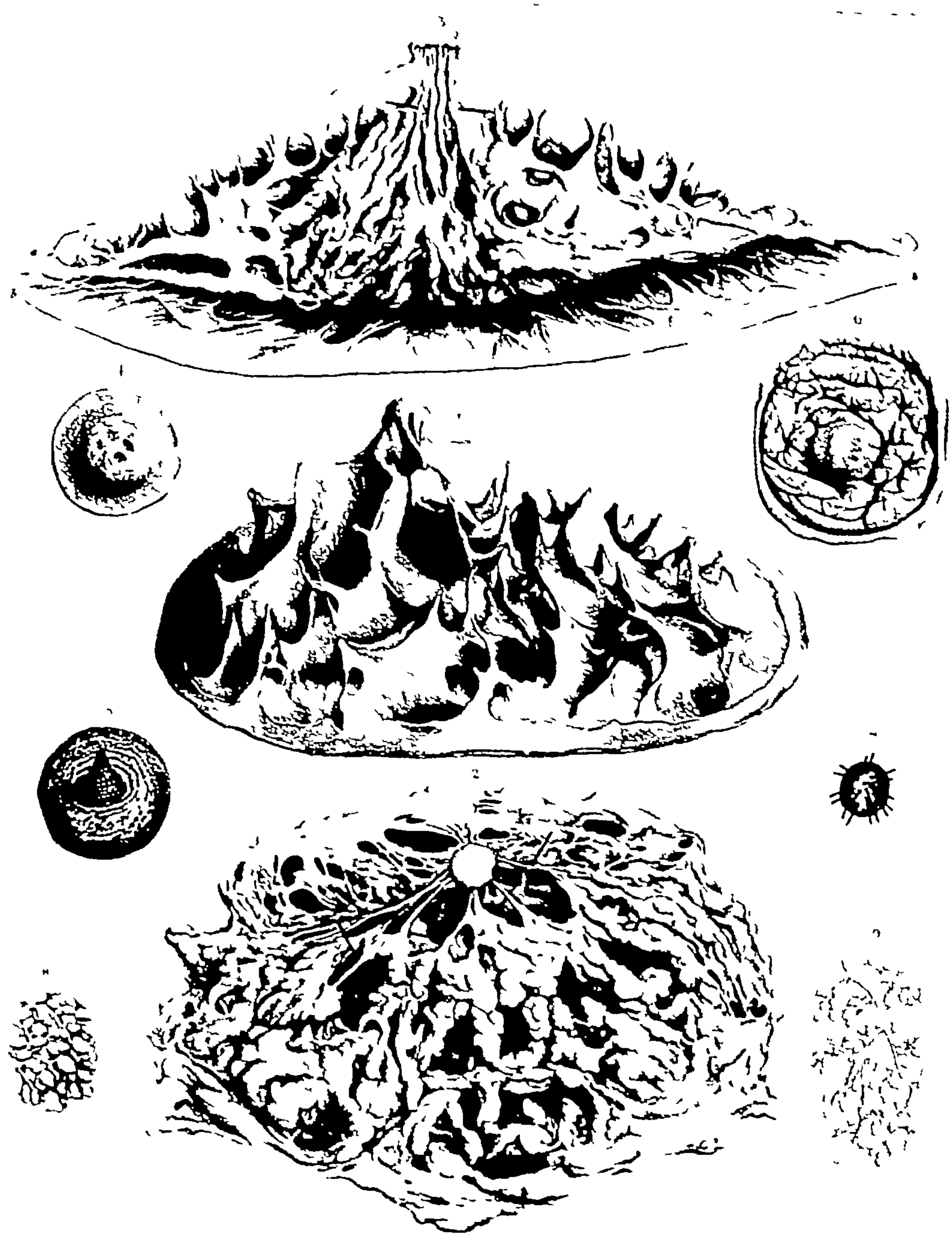

FIG 76 Original illustrations of the suspensory ligaments of the breast from Sir Astley Cooper's book, *On the Anatomy of the Breast*, published in 1840

G Signs of retraction or fixation to the skin or underlying tissue

H Character and mobility of the regional nodes

All patients, in addition to receiving a thorough breast examination, are given a careful general physical examination with special emphasis on well-being, cardiovascular status or suggestive evidence of remote metastases Examination of the abdomen and pelvis is particularly important A routine roentgenogram of the chest should be obtained in all cases of a definitely determined breast tumor X-ray studies of the skeletal system are not routinely indicated unless the patient complains of regional pain or difficulty in walking (see Chapter XI)

Differential Diagnosis

Cancer of the breast must be differentiated from benign breast disease, chronic and acute inflammations the effects of trauma and sarcoma of the breast as well

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Fig 77 Fibrosis and shortening of the suspensory ligaments of the breast giving rise to marked retraction of the nipple or dependent portion of the breast

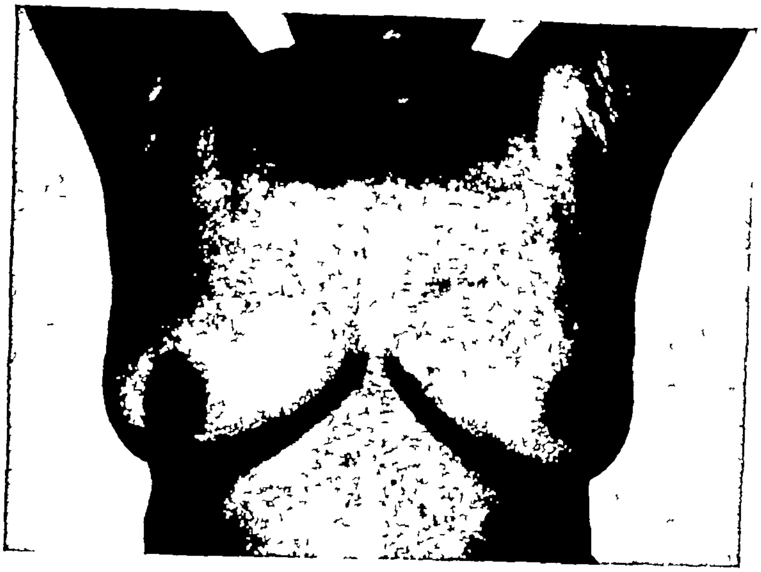

Fig 78A

Fig 78B

Figs 78A and B A Both breasts appear to be deceptively innocent B However, at the *costomammary* fold there is a large and ulcerated breast cancer

Lactation Mastitis

Acute inflammation occurring during or immediately following lactation may resemble inflammatory carcinoma so closely that a differential diagnosis based upon clinical signs and symptoms alone cannot be made The breast is swollen, hard and tender or quite painful, and the skin is red, edematous and warm Axillary adenopathy may occur in either condition The systemic appearance of the patient associated with chills, fever and leucocytosis favor the diagnosis of lactation mastitis A therapeutic trial with the antibiotic agents often reveals the diagnosis and prompt improvement can be expected With localization of the disease, prompt incision and drainage is indicated

Plasma Cell Mastitis

Plasma cell mastitis is a rare disease of unknown origin which closely simulates breast cancer It often begins suddenly with pain, tenderness, diffuse swelling of the breast and mild constitutional signs and symptoms The acute phase soon subsides, leaving a residual area of breast induration with signs of fixation to the surrounding tissue and axillary adenopathy On clinical signs alone the disease often masquerades as a mammary malignancy Resolution is slow and may require several weeks or months for

the disappearance of the firm tumor within the breast

The clinical course of the disease is particularly helpful in the differential diagnosis between inflammatory carcinoma, diffuse anaplastic breast cancer hematoma and plasma cell mastitis Slow resolution is the byword of benignancy

Sclerosing adenosis

This rare but confusing benign breast disease is often regarded with clinical and histological suspicion Its diagnosis depends upon both relevant historical data and a characteristic microscopic appearance. The recognition of this benign disease is particularly important in young women where it may prevent extensive and needless surgery

Tuberculosis and Chronic Infections

A painless localized mass (cold abscess) in one breast is usually the initial sign of tuberculosis It enlarges slowly over a long period of time and ultimately becomes fixed to the skin ulcerates and discharges pus Although considerably less frequent today than formerly tuberculosis of the breast is usually secondary to an acid fast infection elsewhere in the body

Tuberculosis and breast cancer can and do occur simultaneously but this is very rare The author has seen one such patient in whom a tuberculoma and breast cancer coexisted The tuberculous abscess may appear in the parasternal region presumably by extension from the rib mediastinum pleura or lung A recurrent breast abscess with multiple sinuses should be regarded with high index of suspicion Acid fast stains or animal innoculation of the purulent discharge should confirm the diagnosis Caseation is not uncommon

Syphilis of the breast usually occurs as a chancre of the nipple but secondary or tertiary lesions may also appear Fungus diseases, parasitic diseases and other chronic infectious diseases are extremely rare

Traumatic Injuries

Hematoma Post-traumatic breast tumors are usually hematomas and may be exceedingly difficult to distinguish from cancer A deep-seated hematoma may be hard tender and fixed to the surrounding tissue In these respects it mimics breast cancer; however, it is almost always preceded by a definite history of injury and promptly followed by the appearance or discovery of a painful breast tumor A history of bruising or the presence of ecchymosis is usually noted Axillary adenopathy may not be significant The shadow cast by a hematoma is very opaque to transillumination

Fat necrosis Fat necrosis is a rare tumor of the breast usually occurring in the superficial adipose tissue It may or may not be associated with a specific history of remembered or well recognized injury The clinical signs and symptoms are identical with breast cancer Pain may or may not be present The breast tumor is hard fixed and presents the characteristic signs of retraction Clinical caution demands that the diagnosis be confirmed by biopsy

Sarcoma

Sarcoma is a relatively uncommon malignant tumor of the breast (see Chapter XI) Although its age range overlaps that of breast cancer it appears to be more common among younger women The incidence of sarcoma is less than one per cent of all breast malignancies The two predominant types of sarcoma are (1) fibrosarcoma which is derived from the fibrous tissue stroma and (2) adenosarcoma which contains scattered epithelial elements Malignant change in a cystosarcoma phyllodes occurs in about 20 per cent of these otherwise benign giant fibroadenomas

Sarcoma is a rapidly growing tumor which reaches a large size but rarely causes enlargement or metastasis to the axillary nodes These tumors are usually softer than most breast cancers, characteristically lobulated and when in a thin or atrophic breast are

readily recognized as a prominent irregular protuberance Ulceration may occur but skin fixation is rare In sarcomas secondary to pre-existing fibroadenomas, the patient may have noticed a tumor of stationary size for a period of many years Pain and rapid growth may be the first important danger signal

Clinical Stage-grouping of Breast Cancer

Based upon the findings during physical examination, the International Congress of Radiology has recommended the following clinical stage-grouping for cancer of the breast This classification is modified after Portmann (77) and is recommended as simple and convenient

Stage I Skin fixation absent or incomplete,
Muscle fixation absent or incomplete,
Nipple may be retracted,
No axillary nodes palpable

Stage II Primary tumor as in Stage I,
Axillary nodes palpable but movable

Stage III· Skin fixation complete, or muscle fixation complete, or axillary nodes fixed

Stage IV Skin involvement wide of tumor, or separate skin nodules, or complete fixation to chest wall, or distant metastases present (including supraclavicular nodes)

Physical findings and clinical staging revealed by examination are recorded prior to treatment The presence of two or more signs characteristic of a particular stage does not affect the grouping This useful method of stage-grouping is favored for the classification of all cases of breast cancer The stage should be recorded in the history at the time of completion of the physical examination

Clinical stage-grouping of breast cancer is desirable not alone for the purpose of a more precise comparison of different series of cases, but also for a simplified classification of operability Unfortunately, similar conventions are not accepted throughout the world In England the Manchester system is generally used. In stage I the tumor is confined to the breast, in stage II, the axillary nodes are involved, in stage III, the tumor is still regional but is extending beyond the breast as evidenced by fixation, and stage IV denotes remote metastases or extensive disease

The Steinthal (86b) classification, designed many years ago to further prognostic accuracy and to provide a satisfactory basis for study of end-results, depends principally upon a clinical estimate of the degree of axillary lymph node involvement It has the disadvantage of employing only three stages

Portmann (77a) has proposed a revised clinical-pathological classification utilizing, as one of the major criteria, the degree of axillary lymph node involvement determined by microscopic examination

Stage I· Skin not involved
Tumor localized in breast and movable
Metastases none in axilla or elsewhere

Stage II Skin not involved
Tumor localized in breast and movable
Metastases few axillary lymph nodes involved, no metastases elsewhere

Stage III Skin edematous, brawny red induration or inflammation obviously not due to infection, extensive ulceration, multiple secondary nodules
Tumor diffusely infiltrating breast, fixation of tumor or

breast to chest wall edema of breast secondary tumors
Metastases many axillary lymph nodes involved or fixed, no clinical or roentgenologic evidence of remote metastases

Stage IV Skin as in any other stage
Tumor as in any other stage
Metastases axillary and supraclavicular lymph nodes extensively involved clinical or roentgenologic evidence of metastases

Clinical stage-grouping based upon pathologic examination of the axillary nodes unfortunately can only be applied to patients who have undergone radical mastectomy This in turn makes staging directly dependent upon the extent of the operation and the diligence skill and patience of both the surgeon and the pathologist However the value of staging is primarily clinical It should allow the surgeon radiotherapist or oncologist to assess the advancement of the disease and to determine the most desirable therapy

There would be definite advantages in reaching some international agreement on definitions for the stage-grouping of breast cancer Smithers and his colleagues (86a) in an admirable study of this subject recommend five clinical stages which are as specific and precisely defined as clinically possible Five divisions allow for a sharper definition and distribution of patients over the range of breast cancer advancement This is essential when evaluating absolute survival rates, as it reduces the unintentional error in the so-called "comparable series."

Although it has long been known that breast cancer may spread by way of the internal mammary lymph node chain (see Chapters II and XII) this extension has never been taken into consideration in either clinical or pathological staging Recently however Handley and Thackray (40a) have classified their 150 cases of breast cancer in whom internal mammary node biopsies have been performed into three rather unique groups in accord with the following Stage I when the tumor was confined to the breast Stage II when the tumor remained within the limits of radical mastectomy, and Stage III when the tumor had spread beyond the limits of radical mastectomy Without knowledge of the state of the internal mammary nodes it is obvious that a Stage III case could be readily and incorrectly classified as Stage II or even Stage I

TABLE 28

	Clinical	Pathological	
		Without internal mammary node findings	With internal mammary node findings
Stage I	79	57	49
Stage II	63	85	52
Stage III	8	8	40

The striking results of Handley and Thackray's biopsy study on staging are shown by table 28 (reported as number of cases)

The appalling inaccuracy of clinical staging is all too evident by these figures In regard to the effect of internal mammary node biopsy on pathologic staging there appears to be only a slight difference in Stage I However the discrepancies in Stage II and Stage III are astounding The down staging in Stage II from 85 to 52 and the upstaging in Stage III from 8 to 49 as the result of internal mammary lymph node biopsy is a real challenge to our current concepts of classification and therapy Margottini and Bucalossi (63b) and Andreassen and Dahl Iversen (5a) have shown that 23 to 33 per cent of patients with axillary metastases show histological invasion of non palpable supraclavicular nodes as well

Criteria for determining the clinical stages of breast cancer should be based upon a careful physical examination supplemented when necessary by simple instrumentation which is available to all physicians The following code for the clinical staging of all accessible tumors is recommended by both the American Cancer Society and the International Union Against Cancer Despite its separate and distinct classification of the primary tumor and its regional metastases, this code is generally similar to the more specific previous classification Although clinical staging compared to pathologic staging by means of one code or another still may be inaccurate, it is the least inaccurate clinical method available In the opinion of the author the following classification appears simple and most satisfactory

Primary Site

0 No tumor
I Tumor infiltrating the primary organ site
II Tumor of relatively larger size, infiltrating the primary organ site and not extending beyond the adjacent soft tissues
III Tumor widely infiltrating the primary organ site and extending to neighboring organs
IV Tumor extensively involving adjacent soft tissues or organs

Metastases

0 None
I Regional lymph nodes slightly enlarged, discrete and movable
II Regional lymph nodes considerably enlarged, and fixed either to one another or to adjacent structures
II A Clinical stages confirmed microscopically

Patients clinically diagnosed and classified as operable (Stage I or Stage II, Primary Site I or II, Metastases I) must be considered as "urgent" candidates for immediate or early hospital admission Delay may be measured in days but never in weeks or months The surgical excision of a breast tumor is *not* an elective procedure but one requiring urgent surgical care

PHYSICAL SIGNS IN LATENT BREAST CANCER

Although every effort must be made in physical diagnosis to detect the dominant tumor within the breast, yet certain occult cancers may first become manifest only by axillary or more distant metastases without demonstrable evidence of a primary tumor As early as 1907, Halsted (38) commented that, "I have twice seen extensive carcinomatous involvement of the axilla due to mammary cancer, which latter in neither instance became palpable or demonstrable for a considerable period after the axillary glands had attained conspicuous dimensions " In each case the enlarged axillary nodes had been removed one and two years before the appearance of the primary breast tumor Examination "made in the most careful manner, failed to find the slightest evidence of cancer in either breast "

Jackson (44) has reported three patients with breast cancer, each of whom had a palpable axillary metastasis with no clinical signs of a primary tumor within the breast Although each of these three patients was examined by several physicians, careful physical examination of the breasts was completely negative However, radical mastectomy confirmed the diagnosis of a small breast cancer in all three patients Cogswell (14) has reported a similar situation in a patient with a hidden breast cancer of less than one centimeter in diameter located deep within the breast An axillary swelling alerted the patient to consult her physician The concept of latent breast cancer has been discussed by Willis (96), and he refers to

several patients in whom the first sign of breast malignancy was axillary or more distant metastases

An excellent study of occult breast cancer has been reported by Fitts and Horn (25) in which these authors reviewed their experience over an extended period of time At the Hospital of the University of Pennsylvania 15 patients were operated upon during an eight year period for latent cancer of the breast without the presence of a palpable mass In a sixteenth patient metastases to the abdomen from an unknown primary tumor of the breast was discovered at autopsy The initial signs of breast cancer in these patients were primarily, (1) nipple discharge, (2) dermatitis of the nipple and (3) axillary enlargement Recognition of occult breast cancer by these physical signs must be augmented by a high index of suspicion

A most interesting and unique patient with breast cancer has been reported by Klopp (50) A large metastatic axillary node was surgically excised 48 months before the clinical appearance of cancer within the breast In this patient *special attention was* given to the breast yet repeated physical examinations failed to discover the primary growth *A latent period of four years is in*deed unusual however the unpredictable natural history or mitotic interval of breast cancer is notorious It is perhaps important to note that the early onset of axillary metastasis in this particular patient could hardly be indicative of rapid progression of the disease Many patients have been seen in whom the primary breast tumor has been neglected or otherwise disregarded until back pain cough or dyspnea has brought them to the physician with extensive osseous or pulmonary metastases

Although most cases of breast cancer fall into the middle ground of average growth rate and tendency to metastasize extremes on either end of the scale of mitotic activity are not uncommon Metastases may be the first evidence of a primary tumor that is barely palpable or on the other hand, a slow-growing scirrhous carcinoma of the breast may "last a lifetime" permitting a patient to live out her normal life span ultimately to die of cardiovascular or other disease It is convenient to consider breast cancer as falling into one of three general groups, as suggested by Hammond (40)

A Those cancers that metastasize when the tumor is too small to be detected by present clinical examination,

B Those cancers that metastasize very late when the tumor is large and quite obvious

C An intermediate type of cancer that metastasizes only after it reaches a detectable size by physical examination

The importance of early diagnosis is of vital concern in those cancers which can be detected and treated before they have spread beyond the reach of surgery Metastases of course, will be inevitable if diagnosis or treatment is delayed All of us however tend to *celebrate our therapeutic triumphs when the* degree of malignancy is low or the host resistance is high.

Exfoliative Cytology

The importance of exfoliative cytology in the early detection of breast cancer lies in the practical observation that a positive diagnosis can be accurately ascertained in a small but definite number of patients with nipple secretion. Cytologic diagnosis (48) or spontaneous biopsy (4) has proved most useful in the diagnosis of early carcinoma in situ of the cervix and obscure pulmonary carcinoma The accuracy of the technique is dependent upon the proper preparation of the slide as well as upon the experience of the examiner

The early diagnosis of intraductal cancer

of the breast associated with incipient Paget's disease has been reported by Eisen and Taft (24) Smears of exfoliated cancer cells found in the nipple secretion led to the diagnosis of breast cancer Nipple discharge was the first and only sign of this latent malignancy Papanicolaou (74) and other clinical investigators interested in exfoliative cytology have indicated that the smear examination of nipple secretion should not supersede routine examination but should merely serve as a valuable adjunct in the detection of the occasional case of breast cancer. The technique is simple, painless, and when positive, of invaluable aid in the early treatment of what might be an otherwise suspicious or silent lesion

Jackson, Todd and Gorsuch (46) have reported a study of nipple secretion in several thousand patients This cytologic investigation was based upon the examination of fluid which was forcefully expressed from the nipple by manual manipulation Milking of the nipple is advised by these authors as a part of the routine breast examination The technique is reported as a diagnostic aid in the detection of a latent papilloma or excessive intraductal epithelial hyperplasia rather than as a test for the diagnosis of cancer Since gentleness is the sine qua non of physical examination, one cannot overlook the fault of this method which is based upon misapplied force

The distinctive advantages and disadvantages of exfoliative cytology have been objectively summarized by Papanicoloau (73) Among the advantages are (1) simplicity and inexpensiveness, (2) reliability in experienced hands, (3) early recognition of latent cancer, and (4) usefulness in large scale screening programs The main disadvantages are (1) diagnostic criteria require standardization, (2) type and origin of cells may be difficult to identify, (3) grade of malignancy remains unknown, and (4) time requirement for cytologic examination is somewhat longer than for the examination of a pathologic section

Saphir (80) has reported his experience in the cytologic examination of breast secretions Most material for study was obtained as a spontaneous nipple discharge or manually expressed from patients having a history of nipple secretion Cytologic examination not only may lead to the early diagnosis of certain cases of breast cancer, but it was found to be helpful in the diagnosis of chronic cystic mastitis or papilloma The clear or serous secretion of chronic cystic mastitis may be devoid of cellular elements or merely show an occasional desquamated epithelial cell Smears showing the presence of phagocytes, foam cells, epithelial debris, or occasional red cells are also characteristic of chronic cystic mastitis In cases of papilloma, clumps of benign tumor cells, red cells and phagocytes containing blood pigment are often present In cases of breast cancer including Paget's disease and especially intracystic papillary carcinoma, red cells, phagocytes and typical cancer cells either singly or in clusters are at times demonstrable

Successful as exfoliative cytologic examination is in the diagnosis of cancer of certain organs, nevertheless it has several shortcomings in the detection of cancer of the breast Aside from the essential requirement of highly skilled personnel, there must be a nipple secretion adequate to allow desquamated cells (within major ducts) to be carefully examined However, in the experience of most breast clinics spontaneous nipple discharge occurs only in 5 to 10 per cent of all patients with breast disease When spontaneous secretion is present, smears should be examined for the occasional occurrence of neoplastic cells as indicated by the Papanicolaou technique

Generally speaking, the early diagnosis of breast cancer offers the greatest hope for suc

cessful treatment Although a practical and efficient diagnostic test for cancer remains to be discovered, exfoliative cytology may be a real aid in detecting early cancer of specific sites Its value as a mass screening procedure is yet to be fully appreciated However, at the Strang Prevention Clinic of the Memorial Hospital, in a group of 560 asymptomatic women undergoing cancer detection examinations breast secretion could only be obtained in 19 per cent of these women despite the use of a breast pump and massage However with the use of a more efficient mechanical breast pump which is now available, the number of satisfactory secretory smears may be increased

Desquamation within the duct system of the breast is rather limited in the resting mammary gland Malignant tumors developing in the larger ducts are more likely to be detected by the cytological method than are those arising in the smaller or more deeply located ducts or the alveoli of the mammary parenchyma

As suggested by Papanicolaou "the clinical application of the cytological method is at present limited to the examination of spontaneous nipple discharge" It is in this group that the cytological examination of breast secretion is of particular value in detecting early or occult breast cancer

The diagnosis of cancer by smears should be based upon substantial evidence offered by sufficiently pathognomic cells and cell groups Final conclusions upon which major decisions must rest demand the unequivocal proof of more than merely a few suspicious cells

TRANSILLUMINATION

The clinical value of transillumination of the breast as a diagnostic aid remains a matter of considerable difference of opinion among competent observers Cutler (18) in 1929 first reported a large series of breast lesions carefully examined by this newly applied method An excellent resumé of transillumination can be found in Cheatle and Cutler's book *Tumours of the Breast* (13) However it is important to appreciate that in common with other diagnostic aids transillumination is an adjunct to physical examination and not a divining rod for diagnostic revelation Whereas some careful clinicians find it only of limited usefulness others employ it routinely and in conjunction with a complete breast examination

The method is based upon the varying translucence and opacity of different types of tissue Correct interpretation of the transillumination findings is based upon a knowledge of the suspected breast lesion augmented by a considerable clinical experience However most clinicians employing transillumination have been unable to differentiate between benign and malignant solid tumors by this technique

Technique

To be most effective transillumination should be done in a dark room with the examiner's eyes adequately accommodated This time and space requirement in itself seriously handicaps the routine use of transillumination The transilluminator should be a cold bright light of sufficient intensity to penetrate the breast tissue I have found the Cameron Enduralite "* lamp with a rubber shield and rheostat to be excellent It enables the intensity of the light to be varied at the convenience of the examiner

With the patient in the sitting position, the shielded light is placed beneath the under-surface of the breast and directed through the breast tissue toward the examiner Pressure over the breast enhances its translucence and may increase visual acuity Tumors that are fixed to the chest

* Cameron Surgical Specialty Company Chicago Illinois

wall or located high in the axillary tail of a closely fixed breast, or deeply situated in a small, flat, non-pendulous breast are not amenable to transillumination Cutler calls attention to the intensity of the light as a most important detail in this technique of examination "The most formidable source of error is the over-illumination of small solid tumors, thus establishing a false translucence " The light is moved about from one area of the breast to another as each region is carefully inspected

Interpretation

Fat is highly translucent and, therefore, large obese breasts transilluminate well Solid epithelial tumors, fibroadenomas and accumulated secretory or epithelial debris within dilated ducts are moderately opaque Blood is intensely opaque Solitary, thin-walled cysts containing clear fluid are highly translucent, however, chronic cystic mastitis is usually diffusely opaque, depending upon the thickness of the tissue surrounding the cysts and the turbidity and character of the fluid Diffuse opacity is also characteristic of deep-seated cancer During lactation the breast is totally opaque The intense opacity of blood itself is more marked than such solid tumors as breast cancer Therefore, transillumination is said to be of considerable value in the differential diagnosis between a traumatic hematoma and a solid tumor, but in my personal experience the shades of difference are subtle and dependent upon many intangible and variable factors

The most striking feature of transillumination is the appearance of the blood vessels or blood itself within dilated ducts In the presence of a papilloma associated with a bloody nipple discharge, transillumination will often accurately localize an impalpable lesion (a sharply outlined shadow of intense opacity), as well as define the duct of its origin in the subareolar area Transillumination, however, is only of limited help in determining whether the source of bleeding is a papilloma or a cancer

In the clinical interpretation of transillumination, "it is better to understand a little than to misunderstand a lot." For what may appear to be benign by the light of the transilluminator may prove to be malign by the light of the microscope The danger of cancer is ever present, whereas the danger of diagnostic misinterpretation is never absent Yet, despite the serious drawbacks of this diagnostic aid, we should not be deterred from employing transillumination for localization as well as differential diagnosis whenever the clinical condition deems it advisable

Diagnostic X-Ray Examination of the Breast

Roentgenographic studies of breast tumors have been widely explored, but there is no general acceptance of their diagnostic value Past failures have been blamed on faulty technique, inexperience, and the low order of diagnostic correlation between X-ray and histologic appearances

Since the pioneer studies of Warren (90), Dominguez (21), Seabold (82), Hicken (42), and Lockwood (57), among others, there have been described more modern and improved techniques of examination by Leborgne (53), Gershon-Cohen and Ingleby (28) and Gros and Sigrist (35) Due to the complex pathology of breast diseases, as well as to the small difference in X-ray opacity between normal and abnormal tissues, the advantageous use of roentgen study requires a precise technique

It is claimed by enthusiasts that an expert X-ray examination of the breast will reveal a reliable diagnosis by simple mastography in 90 per cent of patients with breast tumors However, Leborgne, with straightforward sincerity, states "We are now usually able to individualize the different images neces-

sary for a precise diagnosis of the mammary parenchyma. Contrast mastography consists of the intraductal injection of an opaque contrast media for the more accurate definition of breast disease by roentgenography This procedure is not without its obvious dangers

Whereas X ray examination may be of limited diagnostic value in selected patients (the presence of punctate calcifications is regarded as a sign of malignancy) in my personal experience the technical and interpretive pitfalls render roentgenographic examination an unrewarding expense

Clinical Use of Radioactive Isotopes in the Diagnosis of Cancer of the Breast

Phosphorus is a ubiquitous metabolite which concentrates differentially in various tissues Organs with a high metabolic activity and a rapid growth rate appear to concentrate the element phosphorus in larger amounts than do organs with a low order of cellular activity This differential selectivity can be readily demonstrated by the administration of the radioactive isotope P^{32}

The clinical use of radioactive phosphorus in distinguishing between benign and malignant breast tumors by their relative isotope uptake has been carefully investigated and reported by Low Beer (59) Although the technique has serious limitations of both a physical and biological nature yet the surface measurement of radiophosphorus uptake in breast disease constitutes a new and interesting adjunct to our diagnostic armamentarium

A differential concentration of P^{32} greater than 25 per cent as compared with normal breast tissue indicates the possible presence of breast cancer In patients with breast cancer the accuracy of this test is said to be relatively high A differential concentration of P^{32} greater than 150 per cent as compared with normal breast tissue indicates an inflammatory disease Low Beer also suggests that this method may prove useful in following changes in tumor growth associated with castration or hormone administration Progression of cancer growth may be associated with increased P^{32} uptake while regression may be associated with a decreased P^{32} uptake The merit of this type of clinical investigation lies in its unique biophysical application and novel approach to a difficult diagnostic problem Sound surgical judgment however cautions us against this technique as a reliable substitute for surgical biopsy

Similar studies have been carried out by Baker and his co-workers (9) using radioactive potassium (K^{42}) The selective uptake of this isotope by breast cancer appears to correlate most closely with the size of the tumor None of the benign diseases including a tuberculous abscess of the breast revealed any degree of selective concentration of K^{42}

Stirrett and his associates (87a) advocate the routine use of hepatic radioactivity surveys in both the preoperative evaluation of all patients with suspected metastatic cancer and the follow up examinations of these patients after radical mastectomy The use of radioactive iodinated (I^{131}) human serum albumin offers a safe and accurate method of determining the presence of hepatic metastases provided these lesions are at least 2 cm in diameter and provided the patient is free of ascites, inflammatory processes in the liver and intra abdominal inflammatory lesions.

The future advances in the medical application of atomic energy may dazzle even the most imaginative—for the 'glories of the possible are ours Nevertheless until the realization of these things unseen we must rely upon the commonplace triumphs of past experience

FIG 79 Infra-red photograph revealing dilatation of the superficial veins of the left breast, especially in the superior-lateral aspect A large cancer was present in the upper and outer quadrant

Infra-red Photography in Diagnosis

Since the essential need for early diagnosis remains readily apparent and of paramount importance, there have been many unique facets of clinical research applied to the problem of breast cancer As the result of years of clinical investigation, Massopust (65) has intensively studied by infra-red photography the superficial veins of the thorax in relation to tumors of the breast (66) (figs 24 and 79)

A number of research investigators throughout the world have been working independently upon diverse problems related to the application of infra-red photography to genetics, pregnancy, venous abnormalities and malignancy Results have not always been uniform or conclusive and speculation has arisen regarding the basic factors involved in the physiochemical response to infra-red radiation Gorman and Hirsheimer observed "There is a marked dissimilarity of venous pattern among all the subjects photographed "

In the study of Anson, Wright and Wolfer (6), as well as in Chapter II, it was emphasized that in the arterial blood supply to the breast these vessels do not reach the gland from the inferior aspect but approach it only from the medial and superior-lateral aspects Phlebographic evidence of the principal pathways of venous drainage by infra-red photography is generally in accord with these conclusions Massopust's (67) study indicates that there is "a wide divergence in the predominant convergence of the superficial veins of the thorax" which implies that there is some variation in the principal drainage areas of the breast These venous patterns have been classified in specific groups

In certain cases of breast disease the appearance and pattern of the superficial veins of the thorax, as graphically portrayed by infra-red photography, were considered to be obviously altered It has been suggested that this method of infra-red photography might serve as an additional diagnostic adjunct in the detection and differential diagnosis of breast cancer

Ultrasonic Waves in the Differential Diagnosis of Breast Tumors

Ultrasonic waves are sound waves of very high frequency Similar to other types of sound waves, their speed through air or through tissue varies with the density of the media The principle of creating ultrasonic impulses and studying the returning echoes has been used in industry for many years for

the detection of flaws in metals. In the field of medicine Ludwig and Struthers (61) demonstrated that gallstones or foreign bodies could be detected by this type of simulated radar Intracranial tumors have also been detected by ultrasound (26 27)

Encouraged by striking differences observed in the echo patterns of malignant versus-normal tissue Wild and his co-workers (93 94) have intensively investigated the use of ultrasonic pulses and their diagnostic possibility in tumors of the breast In a clinical study of 21 patients examined prior to operation with both benign and malignant breast tumors, there was good agreement between the echographic diagnoses of cancer and the microscopic diagnoses However, two patients with fibrocystic disease were diagnosed incorrectly by ultrasonic examination

Great technical improvements of the present apparatus are to be anticipated and in the future it may be possible to apply these principles of ultrasonic echoes harmlessly and with precision to the detection of tumors of accessible areas or organs Until the realization of this speculation the keystone of breast cancer detection and diagnosis must rest upon a careful and thorough physical examination

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CHAPTER IX

Breast Biopsy

Introduction

Among the aphorisms ascribed to Sir William Osler is the practical observation that 'medicine is a science of uncertainty and an art of probability " Equally as practical a precept among surgeons is the tenet that proper treatment of breast tumors is absolutely predicated upon a precise pathologic diagnosis The method for obtaining this definite microscopic evidence is by *biopsy*—the removal of a piece of living tissue for diagnostic purposes

It is certainly true that some surgeons of long experience are often quite expert at the reliable recognition of questionable tissue by gross pathologic appearance at the operating table For these practiced masters (and for those concerned with the clinically obvious case) it has been claimed that biopsy is but a device for delaying decision and 'a refuge for the incompetent and a moral support for the timid (14) However if the coxcomb of individual vanity were to be regularly responsible for the deliberate neglect of biopsy or frozen section diagnosis, I venture to predict that even the most imperturbable of experts would occasionally experience the qualms of a profound surgical humility at having performed an unnecessary mastectomy for what ultimately proved to be on permanent section a benign breast disease For 'things are not always what they seem and gross appearances may be misleading and veiled by subtle treachery

Whereas at the Johns Hopkins Hospital and at other large surgical centers almost all tumors of the breast (except those which are obviously grossly benign) are subject to diagnostic biopsy and immediate frozen section examination prior to definitive surgery to expect a similar situation to prevail in less specialized clinics throughout the country is illusionary In New York state (exclusive of New York city) where cancer reporting is mandatory, Gerhardt and Goldberg (6a) reported that biopsy was performed in only one-third of the cases of breast cancer "However it is not unlikely that a number of these examinations, particularly table biopsies were actually done but not recorded or reported to us ' Yet it is a good omen to note that the rate of breast biopsy has increased with the years. Ewing in his Beaumont Foundation Lectures has said that to "resort to a biopsy is a confession of failure due to clinical inexperience or lack of data from other methods of diagnosis ' However none of us are exempt from this confession of failure regardless of personal expertness or extensive clinical experience

The progressive changes of surgical concepts concerning biopsy are well illustrated by the writings of Halsted In 1898 prior to the routine use of frozen section diagnosis, Halsted (8) cautioned against the excision of pieces of malignant tumors for diagnostic purposes "Breast tumors should not be incised on the operating table prior to their removal The surgeon must learn to recog

nize malignant tumors not only with the microscope but also with his naked eye and fingers" Shortly thereafter, however, Halsted with the aid of Bloodgood began to integrate and more closely apply the benefits of surgical pathology as a sister science In discussing the operation for cancer of the breast in 1907, Halsted (9) regarded biopsy in a more favorable light "Occasionally, and happily with increasing frequency, an incision for diagnostic purposes has to be made Great care should be exercised to make these exploratory cuts no deeper than is absolutely essential"

The concept that there is an increased invasion of the blood and lymph vessels incident to biopsy, trauma and vigorous palpation which would invariably result in widespread dissemination of cancer is difficult indeed to demonstrate There is strong evidence to suggest, however, that factors of host resistance and tissue hospitality are of equal importance in the process of metastasis to those of a simple mechanical-circulatory nature (4) It is likely that malignant cells are scattered throughout the body by the blood or lymph vascular system in numbers which far exceed their ultimate survival as multiple foci of metastases Tumor embolism is not necessarily metastasis

The theoretical or real hazards of breast biopsy have been seriously considered by many clinical investigators (11, 20, 21) but today they are regarded as a prudent and justifiable risk Reliable evidence of survival statistics which depends upon uniform and comparable series of cases, with and without biopsy, is almost impossible to obtain Therefore, despite its recognized potential danger, biopsy remains an expedient and practical necessity which requires the skill of surgeon and pathologist alike in a conjoint clinical operation In carefully incising this thin ice of possible cancer dissemination our surgical safety depends upon a sparing and gentle scalpel

Methods

The following techniques of biopsy and immediate microscopic examination are most often employed for breast tumors

A Aspiration or trephine biopsy
B Excisional biopsy
C Incisional biopsy

Aspiration or Trephine Biopsy

Aspiration or needle biopsy was originally described and advocated by a group of resourceful investigators (13) at the Memorial Hospital of New York The technique is recommended as advantageous by those who use it because of its simplicity and speed in securing a diagnosis It is also advocated as expedient in preventing the lavish exchange of sterile operating room drapes, gowns and gloves which may be required during a routine surgical biopsy The procedure is often performed before the patient reaches the operating room and has even been carried out in the out-patient department or a surgeon's office This latter procedure, however, appears to be contrary to the patient's best interest despite the fact that occasionally it may serve to prevent the expense of a hospital admission for benign breast surgery

Through a small area of local anesthesia the skin is incised with a bistoury or sharp pointed scalpel A large-gauge regular needle or special biopsy needle attached to a tight-fitting syringe is inserted directly into the tumor Suction is exerted on the syringe and a core of tumor is drawn into the needle Maintaining suction in the syringe, the needle is withdrawn slightly and then pushed forward again at an angle to its previous direction so as to cut off the thread of tissue within the needle The biopsy thus obtained is quickly smeared and stained and a diagnosis may be promptly made

Although this technique appears to be less troublesome than the standard surgical procedure, yet even in the hands of skillful and experienced surgeons (1) a correct diagnosis

FIG 80 Intracystic papilloma A false negative diagnosis by aspiration biopsy is readily possible in the case of a similar type of malignant lesion (intracystic papillary carcinoma) A F I P Neg Acc No 218758-C1 (Used with permission of F W Stewart M.D *Tumors of the Breast* Armed Forces Institute of Pathology 1950)

can be expected in only 80 to 95 per cent of the cases of breast cancer This relatively small margin of error is particularly dangerous because it comes so near being correct

Several reasons which are often given to account for failure in the technique of aspiration biopsy are as follows

1 Tumor tissue is not obtained by the needle (particularly in small lesions)
2 Consistency of tumor tissue is too dense and firm to allow adequate aspiration biopsy
3 Error in pathologic interpretation of so small an amount of tissue or of a poor specimen
4 False *negative diagnoses possible in* cases where chronic cystic mastitis and cancer are coexistent (fig 80)

It is apparent even to the enthusiasts of this method that a negative needle biopsy for breast cancer indicates no more than that the patient must be subsequently taken to the operating room for a formal surgical biopsy

Most pathologists without experience and unskilled in this technique of biopsy will be *handicapped and inapt in diagnosis for they* will be forced to rely upon cytology rather than the histologic pattern in observing microscopic appearance This may prove to be particularly difficult and dangerous in well differentiated papillary or border line breast tumors The hazard of the masquerading malignancy adds to the limitations of this method of biopsy

Reasonable indications for the use of aspiration biopsy are as follows

1 Confirmation of clinical diagnoses in patients who are considered inoperable or who are candidates for only hormone or radiotherapy

2 Confirmation of a clinical diagnosis prior to preoperative radiotherapy

3 Confirmation of a clinical diagnosis prior to the contemplated interruption of pregnancy

4 *Therapeutic aspiration of a galactocele* developing during pregnancy or lactation

5 Confirmation of recurrent or metastatic cancer in patients where the diagnosis cannot be established by other means

6 Immediate confirmation of a clinically obvious cyst purely as a palliative procedure in a patient who is in pain or apprehensive about cancer However early hospital admission and surgical excision must be performed regardless of the results of aspiration

It is to be noted that Robbins Brothers, Eberhart and Quan (14a) reporting on 1 576 cases of cancer from the Breast Service of the Memorial Hospital indicated that

"one hundred and thirty-three of the patients whose diagnosis of carcinoma of the breast was first established by frozen-section examination following local excision of the tumor *had had an inconclusive or negative aspiration biopsy originally*" (Editor's italics) However, these investigators concluded that aspiration biopsy per se seemed to have no effect on the long-term survival rate in their follow-up studies

The use of fluid aspiration alone as a diagnostic and therapeutic procedure for chronic cystic mastitis has been advocated by several reliable investigators It is recommended by these surgeons as a practical and expedient method for the diagnosis and treatment of benign cysts which will avoid an unnecessary hospital admission and operative surgery However, despite the most rigid precautions the performance of this dangerous procedure carries with it an unjustifiable risk

Trephine biopsy (3, 10), which has been used extensively in the Scandinavian countries and elsewhere on the continent, has many of the good and bad features of needle biopsy The trephine is rotated by means of a small but powerful electric motor and the ordinary bore is somewhat larger than a biopsy needle By this turbulent technique the trephine may accidentally (and very occasionally does) perforate a large vessel or even enter the chest wall carrying cancer cells along its course If one of the essential factors responsible for *cancer dissemination is a high tissue pressure, then the ill-advised use of such force as may be required in trephine or aspiration puncture is definitely contraindicated* Atkins considers that "drill biopsy had better be left to those who have a particular skill, a peculiar disposition, or a poverty-stricken comprehension " Cannula biopsy (15) by means of a pair of forceps which pass down the center of a small trochar to bite a piece out of the core of a tumor is an ingenious technique which is seldom used in America

Excisional Biopsy

There is a wide difference of opinion among surgeons the world over as to the relative merits of *excisional versus incisional* biopsy (1, 7, 16, 17) In a recent sample survey of leading breast clinics the consensus favored excisional biopsy of most breast tumors except those which were large or diffuse However, agreement even within individual clinics was seldom uniform

The complete but gentle surgical excision of a *small* (2–4 cm) or obviously benign breast tumor, including an adequate margin of so-called "normal" surrounding tissue, is almost a faultless procedure Despite the invisible advance of infiltrating tumor cells considerably beyond the point of macroscopic permeation, total excisional biopsy of a *small* breast tumor is a prudent necessity The pathologist is thus provided with an adequate specimen for gross examination and selection of tissue for diagnostic purposes, and the need for additional tissue and repeated biopsies is precluded The degree of risk involved in excisional biopsy is small but unavoidable and far outweighed by the accuracy of diagnostic information The potential danger is particularly trifling if the tumor is *immediately* submitted to frozen-section examination and a radical mastectomy is promptly performed when indicated

Incisional Biopsy

Incisional biopsy and an immediate frozen-section diagnosis is the method of choice in most suspicious tumors of the breast As noted by Horn (see chapter V), the primary purpose of a frozen-section examination is the furnishing of information which will influence an operative procedure already under way A pathologist skilled in this technique of rapid microscopic examination can be of

indispensable assistance to the surgeon and of equal benefit to the patient. A distinguished Mayo Clinic pathologist, Malcolm B. Dockerty, has recently said (5) that "with the exception of cortical bone and teeth there is no solid tissue which cannot be cut, stained and mounted for microscopic examination under an oil immersion lens—all within a minute or two of the time of its surgical removal from the human body. No less is it a fact that with the use of polychrome methylene blue stain there are no endogenous solid tissue elements which are not as clearly demonstrated as with the routine hematoxylin and eosin preparations made after 24 hours of fixation." Dockerty has described (6) in step-by-step detail the technique of frozen-section examination designed to yield the best and most consistent results. "In the hands of a technician familiar with its details it can be expected to achieve the following objectives, namely: 1) rapidity—not more than 60 seconds being required to prepare, cut, mount and stain a section from the average block of tissue; 2) uniformity and thinness of the sections to a tolerance which permits of their being routinely examined cytologically with the oil immersion objectives of the microscope; 3) universal application to sectioning of practically all solid and semisolid tissues of the body (bone and teeth are exceptions to the rule; endometrium, colonic polyps, cortical brain tissue, and lymph nodes *are not*); 4) elimination of all preliminary treatment of tissue, such as formalin fixation, boiling, drying, or other dilatory hocus-pocus."

This method of rapid examination which requires special experience in technique and diagnosis finds its most essential role in large urban hospitals with heavy surgical schedules, yet it can be used with profit in all but the smallest community hospitals. In the absence of this relatively simple equipment the definitive treatment of breast tumors should not be undertaken in those hospitals with limited facilities or without the affiliated services of a properly trained pathologist.

Incisional biopsy is almost always performed under general anesthesia in the main operating room with the patient prepared and draped for possible radical mastectomy. Draping the patient for radical mastectomy may require an additional expenditure of perhaps 10 or 20 minutes of operating room time which should be allowed for in posting the patient on the schedule. Local anesthesia increases the patient's apprehension unnecessarily and is to be avoided whenever possible.

In occasional instances of equivocal and less well defined breast lesions (or during pregnancy and lactation) (see chapter XVII) it may be permissible to perform a preliminary breast biopsy under either local or intravenous anesthesia. Frozen-section or permanent-section diagnosis should be followed by an urgent request for accelerated or immediate hospital admission if required. This procedure, if cautiously employed in selected cases, might well encourage physicians to favor biopsy of early lesions in preference to "watchful waiting."

Perhaps among all the accomplishments of a sound surgical training there is none preferable to a light and gentle touch. This applies equally to the preparation of the skin as well as to the handling of the scalpel. The vice of unbounded vigor in "painting" the breast for biopsy is an all too common abuse among the young and inexperienced house-officer. In the ardor of the preoperative preparation the intern or assistant resident may soon forget the principles of gentleness and the possibility of tumor emboli. Violent massage with the sponge stick does the justice of even the most meticulous mastectomy a grievous injustice. Also, the reckless and extravagant application of towel-clips al

though less serious than roughness, makes for a painful convalescence needlessly

It is a principle of correct conduct as well as a legal responsibility to obtain consent for radical mastectomy prior to biopsy Failure to obtain consent for a specific operation constitutes a trespass in addition to a breach of moral integrity and professional trust The legal protection afforded by signed operation permits which give consent "to perform any operative procedure deemed necessary" may not be without risk Surgeons should not submit a patient to operation without first discussing the possibility of performing a radical mastectomy

Withal, confidence and hope should be constantly inspired and encouraged While allaying fear the truth of the problem must be fairly defined to the patient in a reassuring manner The fine art of comfort is the touchstone of all medical and surgical success As Galen has said, confidence and hope do more good than physics—"he cures most in whom most are confident"

In performing an incisional biopsy a special biopsy tray on a Mayo stand is set up, which spares the instrument nurse and main instrument table from possible cancer contamination (fig 81) A specially folded towel containing compartments for instruments and sutures may suffice Through a small radial incision the tumor is exposed and a wedge of tissue measuring no more than one or two centimeters in diameter is carefully and gently excised Bleeding from this type of incisional biopsy is easily controlled and is usually considerably less than from excisional biopsy The specimen is examined grossly and immediately sent to the laboratory for frozen-section diagnosis All vessels within the wound are then meticulously ligated with fine silk sutures Persistent minor bleeding may be controlled by electrocoagulation The use of electrosurgical cutting to replace the scalpel in biopsy also has been recommended, firstly, because it seals small blood and lymph vessels as it cuts and, secondly, it destroys free and viable cancer cells adjacent to the incision.

By means of frozen-section examination a correct diagnosis of breast tumors by a skilled pathologist should achieve a high degree of accuracy Even the confusing clinical condition of plasma cell mastitis, a major masquerader of mammary cancer, is easily recognized by rapid microscopic examination Sclerosing adenosis, fibroadenosis, chronic cystic mastitis, Paget's disease and even papillary carcinoma, the illusive imposter, are as readily diagnosed by fresh frozen sections as by the average permanent paraffin preparations There are, of course, rare instances in which the interpretation of a frozen section, cut and examined by an expert, can only result in the uncertainty of an indefinite diagnosis Papillary tumors in the periphery of the breast are lesions of this kind Repeated biopsy and rapid examination may be no more illuminating In these exceptional cases the waiting for permanent paraffin sections is a proper and unavoidable impasse If the time lag between breast biopsy and definitive surgery is a mere matter of several days, the delay though undesirable has not been shown to be detrimental to ultimate survival (table 29) However, the mental anguish of the patient and the mounting expense of hospital and operating room costs while awaiting a second operation is a distressing ordeal Nevertheless, regardless of mitigating circumstances, a surgeon should avoid undertaking a radical mastectomy without unequivocal evidence of malignancy

There is a mutual concurrence among surgeons that a judicious breast biopsy of the single, solitary or discrete "lump" is not in itself a great hazard unless undue delay takes place between biopsy and subsequent radical mastectomy (12). However, if delay is

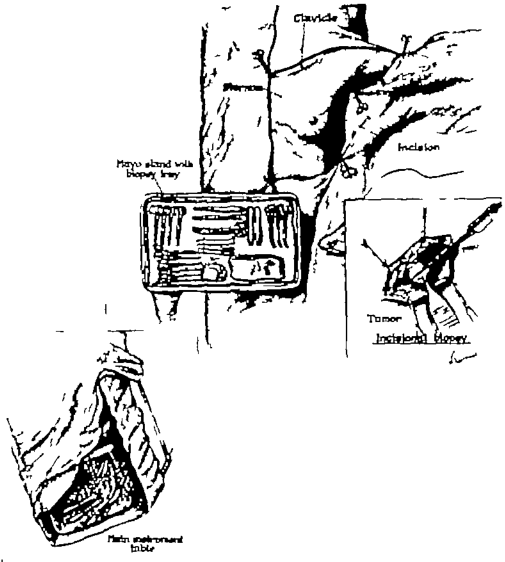

FIG 81 Position of biopsy tray and extent of sterile draping during preliminary procedure Main instrument table is kept covered and free of possible cancer contamination

deliberate and absolutely unavoidable the period of postponement should be measured in hours or days rather than weeks or months (table 29) Time is of the essence and malignancy makes no moratorium There is strong clinical evidence (18) to suggest that simple mastectomy must never be performed in preference to biopsy as an alternative diagnostic measure The shortcomings of subsequent radical mastectomy are indicated by the disappointing end results.

While awaiting word of the frozen section report perfect hemostasis of the biopsy incision is ascertained A surgical colleague has been heard to remark while impatiently waiting for the frozen-section report (requiring an average total time of five or ten minutes) This tumor will metastasize before we hear from the pathologist To expedite and hasten the handling of frozen section biopsies hospitals with a modern flair are installing closed circuit television cables between the central surgical patholog

TABLE 29

Percentage of Survivals after Five Years with Varying Intervals Between Local Extirpation of the Tumor and Radical Mastectomy, and the Percentage of Patients in Stage II at Each Interval Mentioned

Interval	No of Cases	Percentage of Survivals after 5 Years		Percentage in Stage II at Radical Mastectomy	
Max 24 hrs	9	78	81	24	
2–3 days	12	83			
4–14 days	45	74		24	
15–30 days	14	64	60	36	40
>30 days	11	55		45	

(From Acta Chirurgica Scandinavica, Vol XCIX (99) Stockholm, 1950) (13a)

ical laboratory and individual screens in each operating room Black and white televising of frozen sections is perfectly feasible at this time with color television a tempting thought for the near future Two-way communication will allow the surgeon and surgical pathologist the opportunity of discussing the microscopic appearance of the biopsy The practical aspects of this expense remain to be demonstrated.

Every effort is made to prevent blood from seeping out of the wound or through the breast during subsequent radical surgery, thus carrying cast-off cancer cells into the operative field. Contamination of the surrounding skin or drapes should be minimal during the limited operation of incisional biopsy as compared to the more extensive surgery required for excisional biopsy. If the frozen section indicates malignancy, the biopsy incision is carefully closed using a gauze roll or stent over the incision to seal the wound and prevent the danger of leakage All contaminated instruments and drapes are discarded and members of the surgical team promptly change their gowns and gloves The special biopsy tray is removed and the operative field is again prepared for radical mastectomy

Thus, until the development of a clinical laboratory test which would be sufficiently specific to identify *all* breast cancer cases preoperatively and simple enough to be applied expediently, it is well to accept the benefits of biopsy as an indispensable diagnostic aid

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CHAPTER X

A Review of the Surgical Treatment of Breast Cancer

Introduction

In the ensuing years since the notable achievement of Halsted in the field of breast surgery, many skillful surgeons have contributed modifications to the basic principles of his classic operation. Although today radical mastectomy is regarded as a rampart of preservation in most cases of cancer of the breast, yet there has recently arisen among competent clinicians a difference of opinion as to its effectiveness in the treatment of malignant breast disease. Contributing to this contemporary and complex state of doubt and dilemma are a number of conflicting voices of pre-eminence.

Haagensen and Stout (16) have clearly shown that certain advanced cases of breast cancer must be regarded as "categorically inoperable." Pack (44) and his courageous colleagues call for total mastectomy—prophylactic bilateral mastectomy for cancer of only one breast in a disease where the concept of a single focus of malignancy is gradually giving way to the theory of multicentric origin. McWhirter (35), a resolute radiotherapist to the Royal Infirmary of Edinburgh, believes that more lives can be saved in unselected cases by simple mastectomy combined with intensive and superior X-ray therapy. Wangensteen (5)6, Urban (54) (see Chapter XII, Extended Radical Mastectomy), Dahl-Iversen (7), Gordon-Taylor (13) and Gardner (11) fearlessly explore the mediastinum and neck in an extensive thoracocervical dissection known as the super-radical mastectomy. This heroic surgery bordering on "humanectomy" is the contemporary consummation of somatic reduction and "is limited solely by the ability of the human remnant to survive." Its ultimate assessment must await the test of time. The leading exponents of radical surgery are seeking "second look" operations, whereas, Park and Lees (46) have recently intimated that it is extremely doubtful that the survival rate of cancer of the breast is influenced by treatment at all. In commenting upon the difficulties of controlling death from breast cancer McKinnon (34) claims that "the failure of early treatment to reduce (breast cancer) mortality shows that spread of remote metastases occurs before interference is possible." Despite the enlightenment and application of public and professional education, the American Cancer Society estimates that in certain parts of the United States breast cancer is still being treated by inadequate surgery in 25 per cent of all cases.

The Problem and Criteria of Uniformity in End Results

There are few fields in surgery with more pitfalls for the statistically unwary than the appraisal of end results in the treatment of breast cancer. Almost 50 years ago Halsted

(18) commented that "it is especially true of mammary cancer that the surgeon interested in furnishing the best statistics may in perfectly honorable ways provide them. The most conscientious man may refuse to operate upon any but favorable cases."

Real benefit, however, can be derived from a review of the end results of treatment if a great deal of scrupulous care and strict uniformity is observed in recording and reporting clinical studies. In this effort to eliminate the personal "built in-bias" all results should be accurate and intelligible, comparable with similar studies the world over, and indicative of genuine improvement (if such be the case) over alternative methods of treatment or even over the natural life history of the disease itself if no treatment at all was given. The validity of comparative results must be based upon a common language applicable to a specific type of cancer and operative or radiotherapeutic procedure. The selection of cases and criteria of treatment must be uniform. Decisive factors other than treatment do, of course, influence survival and prognosis in cases of breast cancer. The nature of this influence is little known and unpredictable. Such important antecedent factors as are indicated in Chapter VIII (heredity, fertility, age, marital status, pregnancy and lactation) as well as the grade of malignancy, tumor size and location, rate of growth, stage of disease, host resistance and duration of disease present many problems (see Chapter XIV) which must be successfully solved before one can precisely determine the best treatment plan for each patient. As noted by Smithers (51) and his colleagues, "comparisons of overall results obtained in the best treatment centres which do provide the basic data on which absolute survival rates can be calculated show that a steady improvement has occurred over the years but do not yet provide conclusive evidence that the slight differences observed in groups treated at about the same time are due to the treatment methods advocated and not to variations in the material treated." The resolution of the problem of end results and their criteria for accurate comparison will undoubtedly lessen the prevailing world-wide diversity of therapeutic opinion. What now may be regarded as orthodoxy in one clinic is too often considered heresy in another.

Today national and international cancer societies are imploring greater standardization in reporting cancer statistics. It is, of course, most desirable that criteria for determining the clinical stages of breast cancer should be based upon a careful physical examination supplemented by simple instrumentation which is available to all physicians. The code (see Chapter VIII) for the clinical staging of accessible tumors recommended by the American Cancer Society and the International Union Against Cancer is a major move in the right direction. This closely corresponds with the recommendations of the International Congress of Radiology which are modified after Portmann.

A joint committee on reporting cancer end results has recently recommended "Rules for Reporting Five Year End Results of Persons with Malignant Neoplastic Diseases" (table 30). This committee was composed of representatives of the American College of Surgeons, the College of American Pathologists, the American College of Radiology, the American Cancer Society and the National Cancer Institute.

Reliable end results will allow for the comparison of the effectiveness of alternative methods of treatment in achieving 1) permanent cures or 2) prolonging the patient's survival time. Accurate reporting will permit a precise analysis of the influence of such additional factors as histologic type, size and extent of the tumor, duration of the disease

TABLE 30

A Report of Five Year End Results

CANCER OF

This series consists of all patients with cancer of the
both early and advanced, applying to
during the period to

GENERAL SUMMARY	Number of Cases
Total experience—all patients applying	
Section A Cases not previously treated	
Section B Cases previously treated	
Other	
a Applied after treatment elsewhere, no evidence of cancer on admission or thereafter	
b Consultation only, no treatment requested	

SECTION A CASES NOT PREVIOUSLY TREATED

Results at End of Five Years	Number of Cases		
	With microscopic proof	Without microscopic proof	Total
Group I			
c Refused proffered treatment			
d Untraced for full 5 years without recurrence at last examination			
Group II			
e Dead within 5 years of other causes without recurrence of cancer			
Group III			
f Dead, cancer present or died of complications of treatment			
g Dead—presence of cancer unknown			
h Living with cancer present at 5 years			
i Living with condition unknown at 5 years			
j Untraced full 5 years with cancer at last examination			
k Untraced full 5 years, not classifiable in "d" or "j"			
Group IV			
l Living, continuously free of cancer, verified by medical examination at 5 years			
m Living, apparently free of cancer, not verified by medical examination at 5 years			
n Living, successfully treated for recurrence, free of cancer at 5 years			
Total			

TABLE 30—*Concluded*

SECTION B CASES PREVIOUSLY TREATED

Results at End of Five Years	Number of Cases		
	With microscopic proof	Without microscopic proof	Total
Group I			
c Refused proffered treatment			
d Untraced for full 5 years without recurrence at last examination			
Group II			
e Dead within 5 years of other causes without recurrence of cancer			
Group III			
f Dead cancer present or died of complications of treatment			
g Dead—presence of cancer unknown			
h Living with cancer present at 5 years			
i Living with condition unknown at 5 years			
j Untraced full 5 years with cancer at last examination			
k. Untraced full 5 years not classifiable in d or j			
Group IV			
l. Living, continuously free of cancer verified by medical examination at 5 years			
m. Living apparently free of cancer not verified by medical examination at 5 years			
n. Living successfully treated for recurrence free of cancer at 5 years			
Total			

age of the patient and host resistance on the behavior of breast cancer

Reported End Results of Operative Treatment of Breast Cancer

Considering the duration of life following simple surgery for breast cancer Sir James Paget (45) in 1853 reflects the contemporary opinion of the time when he says 'I am not aware of a single clear instance of recovery—of such recovery that is as that the patient should live for more than ten years free from the disease or with the disease stationary'

Yet Samuel W Gross (15) in 1880 a disciple of the teachings and principles of Moore (40) carefully analyzed his own statistics and found about one-sixth of his patients alive and free of disease at the end of ten years His candid conclusions clearly disclose 'that when left to itself carcinoma inevitably kills by its baneful consequences as a local disease or by its remote multiplication

"That about one in six or 16 77 per cent, of the patients die of the operation itself, but that the risk is not so great as to forbid interference since it adds twelve months to the life of the patient

That thorough operation definitely cures 9 05 per cent of all patients or more than half as many as it destroys

The surgeons of an earlier time who have written treatises on the subject of breast cancer made little attempt to carefully fol

TABLE 31

*Early Collective Review of Breast Cancer and the Results of Treatment**

Country or Town	Author	Date	Incomplete				Complete			
			Cases	Lost	Survivors	Per cent	Cases	Lost	Survivors	Per cent
Germany										
Berlin (v Bergmann)	Rotter	1887	109	2	29	27 1	—	—	—	—
	Rotter	1896	—	—	—	—	30	0	11	36 6
	Guleke	1901	704	322	110	28 8	—	—	—	—
Breslau (v Mikulicz)	Scheu	1907 and earlier	150	23	24	18 9	107	16	18	19 8
Heidelberg	G B Schmidt	1889	77	17	17	28 3	—	—	—	—
	Mahler	1900	150	20	35	26 9	—	—	—	—
	Hoffmann	1921	131	0	51	39 0	187	0	65	34 2
Greifswald (Helferich)	Joerss	1897	57	0	13	22 8	35	0	3	8 6
Kiel (v Esmarck)	Oldekop	1879	173	48	27	21 6	—	—	—	—
	Anschutz and Hellmann	1921	—	—	—	—	235	6	120	52 4
Rostock	Schroeder	1905	347	73	85	31 0	183	7	77	43 7
Stuttgart	Steinthal	1912 and earlier	99	0	27	27 3	101	0	34	33 6
Munich (v Angerer)	Gebele	1901	203	13	65	34 2	—	—	—	—
	Frankau	1914	49	6	16	36 5	—	—	—	—
Konigsberg (v Eiselsberg)	Rosenstein	1901	77	26	19	37 3	—	—	—	—
Austria										
Vienna (v Eiselsberg)	Meissl	1904	181	43	38	27 5	—	—	—	—
	Lazarevic	1914	—	—	—	—	238	100	54	39 1
Vienna (Billroth)	v Winiwarter	1878	132	35	8	8 3	—	—	—	—
(Hochenegg)	Finsterer	1904	498	164	97	29 0	—	—	—	—
Graz	Schwarz	1905 and earlier	121	0	38	31 4	35	0	8	23 0
Switzerland										
Zurich	Fischer	1881	54	0	10	18 5	—	—	—	—
	Horner	1894	165	7	58	36 7	—	—	—	—
Rorschach	Wunderli	1906	100	2	22	22 4	—	—	—	—
Norway										
Christiania	Paus	1910 and earlier	6	3	0	0 0	100	27	23	31 5
Italy										
Pisa	Fiori	1909	48	2	27	58 7	21	2	1	4 1
Hungary										
Budapest	Steiner	1906	38	13	1	16 0	22	5	7	11 1
	Dollinger	1908	—	—	—	—	72	11	16	26 2

TABLE 31—*Concluded*

Country or Town	Author	Date	Incomplete Cases	Incomplete Lost	Incomplete Survivors	Incomplete Per cent	Complete Cases	Complete Lost	Complete Survivors	Complete Per cent
England										
London	Butlin and Maxwell	1899 and earlier	177	3	32	28 0	48	0	27	56 2
Birmingham (Barling)	Mills	1921	19	0	10	52 6	150	56	46	48 9
Bristol	Morton	1902	39	1	12	31 5	—	—	—	—
	Morton	1922	—	—	—	—	93	30	30	47 6
United States										
New York	Dennis	1891	84	33	27	51 9	—	—	—	—
	Dennis	1907	—	—	—	—	116	0	59	50 8
New York	Pilcher	1894	23	3	7	35 0	—	—	—	—
	Pilcher	1907	—	—	—	—	17	1	9	56 3
Boston	Greenough and others	1907	(some incomplete)				365	0	105	28 9
	Greenough and others	1921	—	—	—	—	69	6	26	41 2
	Cabot	1907	28	0	5	53 5	14	0	7	50 0
Worcester, Mass	Gage	1905	46	0	11	23 9	—	—	—	—
	Gage and Adams	1911	—	—	—	—	150	1	62	41 6
Rochester Minn (Mayo Clinic)	Judd	1914	—	—	—	—	510	85	210	40 4
	Sistrunk and McCarty	1922	—	—	—	—	218	0	118	53 7
Baltimore	Halsted	1907	—	—	—	—	232	18	89	38 3
Total			4 025	850	924	29 2	3 400	371	1 220	40 3

After Lane Claypon 1924

low their patients Although some clinicians appear to have been aware of crude survival rates the postoperative fate of most patients with breast cancer was unknown The credit for initiating the first systematic follow up survey belongs to Volkmann (55) in 1875 He subjected all of his operative cases first to a careful microscopic examination with the object of establishing the validity of the diagnosis and then he meticulously traced the patients during their period of post operative survival

Lane-Claypon (28) has reviewed and reported a detailed study of the surgical literature of this early period (prior to 1924) (table 31) Because no standard system of classification and survival reporting had been uniformly adopted comparison of results in different countries required a careful scrutiny based upon a personal but precise schedule of analysis

Conclusions which Lane-Claypon drew from this analysis of early results of approximately 20 000 operative cases of breast cancer were as follows

1 After an incomplete or non radical mastectomy for breast cancer of a total of 7 029 patients there was a 29.2 per cent three year survival

2 After a complete radical mastectomy

for breast cancer, out of a total of 8,921 patients there was a 43.2 per cent three year survival.

3. Prognosis following complete operation was greatly affected by the stage of the disease at the time of surgery.

Survival percentage was based upon only those patients successfully followed and did not include those patients considered lost to follow-up. The average five year survival following radical mastectomy for 2,441 patients traced was 33.1 per cent. A partial list of the collected results of the complete or radical operation are reported in table 32. All diagnoses were verified by microscopic examination and, as was the custom of the time, all results except those here noted were recorded as three year survivals.

In an enterprising and unique study of breast cancer as treated in the general hospitals of eight of the largest provincial cities of England and Wales, Lane-Claypon (29) at a later date analyzed the operative results and survival of 1,642 cases of breast cancer verified by pathologic examination. The years selected for inquiry were 1910 to 1913 and 1919 to 1921 inclusive. The type of operation performed was, of course, of the utmost importance. In all stages of the disease except Stage I the radical operation was performed almost without exception whereas in Stage I only two-thirds of the patients had a radical mastectomy. The crude survival rates (the proportion of survivors to the total number of patients operated upon without any deletions) were as follows:

	Survival rate		
Breast cancer	3 years	5 years	10 years
All stages	50.1%	37.4%	25.2%

However, the difference in survival between the first stage of the disease and the other stages of more advanced breast cancer was enormous. The survival rate for the Stage I cases alone was 85 per cent at three years, 78.5 per cent at five years and 73.3 per cent at ten years. These over-all results representing radical mastectomy in England for the period 1910 to 1913 and 1919 to 1921 are remarkably good and compare most favorably with present day surgical accomplishments.

The experience of the Vanderbilt University Hospital has been reported by Brooks and Daniel, Jr. (5). During a 14 year period prior to 1939, 149 radical mastectomies were performed with only one operative death. However, of 72 patients having received a high standard of operative treatment (a sufficient time having elapsed to allow for survival statistics) there were 25 patients (35.5 per cent) alive and well or "cured" at the end of five years. There were 28 patients (39 per cent) alive but not free of disease, which represented the over-all five year survival rate.

Rolf Engelstad (8) reported the results of treatment at the Norwegian Radium Hospital. Patients observed between the years *1932 to 1937 were treated by radical mastectomy* followed by postoperative radium therapy. The absolute five year symptom-free survival rate (all patients included) was 24.1 per cent of 352 patients. It is to be noted that almost 50 per cent of this group of patients were in Stage IV of the disease at the time of treatment. The special character of this hospital weighs heavily against these survival statistics.

The records of 3,105 patients with breast cancer treated in nine large American hospitals were reviewed by Hawkins (21). The *status of these patients was presented in* terms of the variables of treatment, of the state and grade of malignancy, and of the condition of the host. The most important factor in the five year survival rates was the extent of the disease at the time of treatment. When correction was made for the

TABLE 32

*Complete operation All diagnoses subjected to microscopic examination**

Name and Country	Entrants	Died under Three Years			Lost	Alive at Three Years
		Of operation	Of other causes	Of cancer		
United states						
Brown	85	0	0	74	0	11
Cabot	14	0	0	7	0	7
Crile	91	0	0	42	4	45
Davis B Byrom	166	1	0	36	64	65
Deaver and McFarland	200	5	8	45	25	92
Dennis (private)	106	1	0	56	0	50
Gage and Adams	93	2	1	49	1	40
Greenough and others†	365	4	7	240	0	105
Greenough and others	69	0	2	35	6	26
Haggard and Douglass	103	5	0	50	0	48
Halsted	232	4	0	121	18	80
Huntington	13	1	0	10	2	0
Jacobson	71	0	3	33	0	35
Judd	510	0	0	215	85	210
Judd	97	0	0	30	11	0
McCalla	114	0	0	23	0	91
McWilliams	100	4	0	53	26	17
Matas	15	0	2	8	0	0
W Meyer	84	0	0	40	2	32
Oliver	21	0	0	6	0	15
Peck and White	195	6	0	43	75	50
Primrose (5 years)	45	0	0	25	0	20
Rodman (private)	32	0	0	11	0	21
Sadleir	70	0	5	32	0	28
Sistrunk and McCarty	218	1	0	104	0	113
Vander Veer	103	0	0	17	16	70
Warren	102	0	0	79	0	23
Total	3 324	34	28	1 493	335	1 312
England						
Barker	86	5	0	38	9	29
Watson Cheyne	99	0	1	36	4	31
Handley (private)	52	0	0	27	0	25
Leaf	54	2	0	10	2	40
Leech (private)	11	0	1	2	0	8
Leech (hospital)	88	0	8	37	6	21
Mills (private) 6 years	40	0	0	16	9	15
Mills (hospital) 3 years	110	0	0	32	47	31
Monsarrat	36	0	2	8	0	31
Morton‡	93	6	0	27	30	30
Rigby (private)	16	0	0	2	1	4
Rigby (hospital)	62	0	0	14	12	5
Sheild	60	2	0	12	1	21
Total	807	15	12	261	121	286

TABLE 32—*Continued*

Name and Country	Entrants	Died under Three Years: Of operation	Died under Three Years: Of other causes	Died under Three Years: Of cancer	Lost	Alive at Three Years
Germany						
Boss	127	0	0	58	18	51
Hoffmann	187	0	0	119	0	68
Joerss	36	0	1	24	1	10
Lindenburg	183	13	5	81	7	77
Neher	362	16	17	158	7	96
Rosenstein	68	2	0	17	9	1
Salomon	86	1	0	56	0	29
Scheu	107	0	0	73	16	18
Steinthal	101	5	10	52	0	34
Tietze	54	1	0	33	7	13
Total	1,311	38	33	671	65	397
France						
Begouin	133	0	6 (cause ? in 20 cases)	51	38	27
Berard	185	0	0	55	98	32
Delbet	100	0	3	9	72	16
Forgue	285	0	0	170	0	115
Hartmann and Bergeret	328	0	0	120	80	106
Grenade	106	2	4	30	17	53
Heurtaux (4 years)	341	14	17	110	61	139
Lapeyre	225	0	0	26	61	138
Le Dentu	59	0	0	25	0	34
Walther (private)	81	0	0	20	16	38
Walther (hospital)	37	0	0	12	0	25
Total	1,880	16	30	628	443	723
Austria						
Lazarievic	238	4	4	76	100	51
Schwarz	51	3	1	23	0	8
Schwarzkopf	31	3	0	13	6	3
Total	320	10	5	112	106	65
Hungary						
Dollinger	72	3	0	42	11	16
Steiner	22	1	0	9	5	7
Total	94	4	0	51	16	23
Switzerland						
Meyer (Kocher)	212	0	0	146	0	66
Wiesmann	93	0	0	54	0	39
Wunderli	52	0	0	26	0	11
Total	357	0	0	226	0	116

TABLE 32—*Concluded*

Name and Country	Entrants	Died under Three Years			Lost	Alive at Three Years
		Of operation	Of other causes	Of cancer		
Italy						
Flori	23	0	0	20	2	1
Sweden						
Borelius	84	1	0	48	6	29
Brattstrom	205	0	0	136	39	120
Total	370	1	0	184	45	140
Norway						
Paus	100	1	2	47	27	23
Holst (private)	19	0	1	10	0	8
Holst (hospital)	44	0	2	30	3	9
Total	163	1	5	87	30	40
Holland						
Doelman	391	0	0	180	91	120
Kropfeld	56	0	5	24	0	27
Total	447	0	5	204	91	147
Total all countries	9 105	119	118	3 937	1 254	3 250

After Lane Claypon 1924
† 86 incomplete not separable
‡ Some patients recorded among "lost" cases were almost certainly alive

stage of the disease and type of treatment all other factors (age sex color and duration of disease) were found to have little or no influence upon survival

The over-all five year survival rate (all modes of therapy in all stages of the disease) was 23 9 per cent Patients who were lost to follow-up were considered dead of the disease although the author points out the difficulty in summarizing these data The five year survival rate of patients with Stage I breast cancer was 51 per cent

The place of surgery and radiotherapy in the management of breast cancer was thoroughly discussed by Richards (47) Presenting the results of treatment at the Toronto General Hospital during the ten year period 1933 to 1943 he noted a marked variation in criteria of operability surgical technique and survival time even among the single series of surgeons at this noted hospital There were 1 189 patients operated upon by thirty surgeons with an over all five year survival rate of 43 per cent and a ten year survival rate of 26 per cent All patients were treated by radical mastectomy and postoperative radiotherapy A plan of future therapy is recommended in which radical surgery is complemented by pre- and post operative radiotherapy Patients in the advanced stages of the disease are to be considered primarily within the province of radiotherapy

In a thoroughly delightful discussion of

the treatment of cancer of the breast Gordon Gordon-Taylor (13) reminisced regarding his 40 years of experience with radical mastectomy Between December, 1907, and December, 1947, this eminent and eloquent surgeon observed 750 personal patients with primary breast cancer Of this total number only 645 patients were treated by radical mastectomy, the remainder being subject to such clinical selectivity which favored simple surgery or radiotherapy

Using the "ambitious yardstick" of only a ten year survival rate Gordon-Taylor reported 43 per cent of 388 patients (363 operated upon prior to 1929) alive at the end of ten years following radical mastectomy There were 113 patients with Stage I breast cancer in whom the ten year survival rate was 84 per cent, there were 204 patients with Stage II breast cancer in whom the ten year survival rate was 29 4 per cent, and there were 46 patients with Stage III breast cancer in whom the ten year survival rate was 6 5 per cent These extraordinary survival statistics are the striking story of one surgeon's experience dealing "with what might be regarded as a relatively favorable class of case"

The surgical problems involved in breast cancer were ably discussed by Adair (1) in his Moynihan Lecture delivered before the Royal College of Surgeons in 1949 The vast array of clinical material at his disposal at the Memorial Hospital of New York is incomparable "Our experience, philosophy and conclusions are based on the care and study of 13,054 cases of breast cancer at the Memorial Hospital" Adair notes that there are few fields in medicine or science where there is a greater uncertainty in evaluating therapy than in the biostatistics of breast cancer "The method by which some investigators arrive at the statistical results of therapy is quite different from that of another group, making it so that comparisons are impossible" Criteria of operability are also highly flexible and an enthusiastic surgeon may find this borderline a broad and challenging frontier Operability, according to Adair, is interpreted along "very generous standards" at the Memorial Hospital Yet, despite this liberal selection of cases, the over-all survival rate in 3,988 cases (1935 to 1942), including every case, advanced as well as operable, was remarkably good, 39 6 per cent

Consideration of the operable material for the years 1940 to 1942 indicates that the five year survivals in cases treated by radical mastectomy were as follows·

All primary operable cases	58 3%
Breast alone involved	82 2%
Breast and axilla involved	43.5%

Postoperative X-ray therapy following radical mastectomy was administered only to those cases having axillary involvement. It should be noted, however, that these statistics are exclusive of an "indeterminate group" which included among others patients who were lost to follow-up and patients who died of intercurrent disease within five years. Yet, these excellent end results are indeed a tribute to the skill and ability of Adair and his colleagues

At the Radiumhemmet in Stockholm, Berven (3) has reviewed 3,623 cases of breast cancer observed during the period 1921 to 1941 These cases consisted of the following groups·

1 1,164 cases having pre- and postoperative radiotherapy
2 640 cases having postoperative radiotherapy.
3 535 cases with recurrences following surgery elsewhere
4 544 cases having palliative radiotherapy
5 740 cases having no treatment

During the period 1921 to 1935 there were

1 035 patients treated by radical surgery and radiotherapy with a five year survival rate of 46 per cent and a five year "cure" rate of 42 per cent In the period 1936 to 1941 there were 769 patients treated similarly with a five year survival rate of 51 per cent and a five year "cure" rate of 43 per cent There appeared to be no difference in the survival rate between patients treated with both pre and postoperative irradiation and those treated with only postoperative irradiation

Windeyer (59) has recently reported the results of breast cancer treatment at the Middlesex Hospital of London during the years 1936 to 1942 Of a total number of 1 091 patients who applied for treatment 977 were primary patients who had had no previous treatment, and 114 were secondary patients who had received surgical treatment elsewhere. Of the remaining 977 patients, 60 received no treatment whatsoever either because of refusal or advanced disease Follow-up has been excellent (97 4 per cent) and all patients untraced were considered as having died of cancer

Treatment was variable but in general consisted of radical mastectomy in Stage I, radical mastectomy followed by postoperative radiotherapy in Stage II and radiotherapy with or without simple surgery in Stages III and IV

The over-all five year survival rate of 917 patients was 34 per cent and the ten year survival rate was 21 9 per cent In a selected group of "operable" cases treated by radical mastectomy the corrected five year survival rate was 42 9 per cent and the ten year survival rate was 29 per cent These statistics which are representative of one of London's great teaching hospitals almost duplicate those of Lewison Trimble and Griffith (33) reporting their results from the Johns Hopkins Hospital of Baltimore

In an excellent clinical study of 1 042 cases of breast cancer treated at the Radiumhemmet Nohrman (41) reported the end results of treatment for the period 1936 to 1941 Of these patients, 997 were accepted for treatment and 0 9 per cent were men Twenty per cent of the series were considered inoperable Although radical mastectomy was performed in the remaining 767 patients the results of treatment were also computed for an unselected group of 660 patients

The absolute five year survival rate (all patients treated and untreated) was 40 1 per cent The five year survival rate following radical mastectomy was 50 0 per cent for the entire group and 54 7 per cent for the unselected group Preoperative irradiation appeared to have improved the end results in the most unfavorable patients whereas in the remaining patients no significant difference could be demonstrated between the results of treatment with combined pre and postoperative irradiation and with postoperative irradiation alone

The results of radical mastectomy in the treatment of cancer of the breast at the Massachusetts General Hospital of Boston have been ably reported by Taylor and Wallace (53) The five year over-all "cure" rate for the period 1936 to 1941 was 51 per cent In 169 cases the axilla was not involved and the five year "cure" rate was 77 per cent. In 261 cases the axilla was involved and the five year "cure" rate was 33 per cent In computing the "cure" rate all cases submitted to surgery were included except those known to have died of intercurrent disease (without evidence of recurrence) in less than five years after operation Untraced cases and patients with recurrent disease were included but classed as failures. Thus, "cured" cases were those known to be living and free from disease five years following surgery in addition to those dying without recurrence after five years These definitions

as emphasized by Taylor must be clearly kept in mind in comparing survival rates between clinics. However, during the past 50 years there has been a definite and continuous improvement in the results of radical mastectomy at the Massachusetts General Hospital.

Haagensen and Stout (17) have again carefully reviewed the results of radical mastectomy at the Presbyterian Hospital of New York between the years 1935 to 1942 inclusive. Strict and specific criteria of operability which have been published previously guided their selection of cases for radical mastectomy. The fidelity of follow-up was exceedingly good, 96.2 per cent of all patients being followed for five years or until death. Computation was based upon both relative and absolute five year clinical "cure" and five year survival rates. In the analysis of the relative "cure" rates no deductions have been made from the total number of primary cases in which treatment was started. Patients dying of unknown cause or of intercurrent disease, or lost to follow-up before the end of the five year period, were considered dead of breast cancer. Absolute "cure" and survival rates were based upon all patients with primary breast cancer coming to the Presbyterian Hospital.

TABLE 33

	Number	Per cent
Radical mastectomies	495	
Operative deaths	9	1.8
Lost to follow-up	19	3.8
Died of unknown cause before 5 years	7	1.4
Died of intercurrent disease before 5 years	18	3.6
Died of breast cancer before 5 years	151	31.1
Alive, with recurrence at 5 years	47	9.5
Alive, without recurrence at 5 years	241	48.7

After Haagensen and Stout (1951)

The five year end-results of radical mastectomy are shown in table 33.

Thus, the relative five year clinical "cure" rate (without deductions) was 48.7 per cent and the relative five year survival rate was 58.2 per cent. These results represent an improvement of 10 to 15 per cent over the relative rates reported for the years 1915 to 1934.

In this series of critically analyzed cases there were 668 female patients with primary breast cancer who applied for treatment. Only 495 received a radical mastectomy, the remainder either being treated by simple surgery, X-ray therapy or not being treated at all. The absolute five year survival rate (total number of survivors divided by the total number of primary patients) was 47.2 per cent and the absolute five year "cure" rate was 38.6 per cent. The diligent care and exactitude of Haagensen's statistics reflect the merit of his enterprise and ability in the study of breast disease.

A review of all patients with cancer of the breast recorded at the University of California Hospital and Clinics during the 30 year period 1918 to 1947 inclusive was analyzed and recently reported by Shimkin, Lucia, Stone and Bell (49). The clinical material consisted of 1,056 female patients of whom 94 per cent had pathologic verification of breast cancer and 98.5 per cent were successfully followed for at least five years.

The five year survival rate of all patients, 68 per cent of whom already had metastases (Stages II, III or IV) at the time of admission or operation, and including all untreated and untraced patients, was 40.1 per cent. The five year survival rate following surgery was 72.5 per cent for all Stage I patients, 42.2 per cent for all Stage II patients, 18.1 per cent for all Stage III patients with extensive axillary and local disease, and there were no five year survivors among Stage IV patients. Significant differences in survival were considered to be "dependent

upon anatomical extent of the disease at the time of treatment, which is determined primarily by the biologic properties of the neoplasm and possible host-resistance factors, and by the delay from apparent onset to treatment.'

In a carefully computed and rigorously analyzed study of 1 777 new patients with breast cancer seen at the Royal Cancer Hospital in London Smithers, Rigby-Jones, Galton and Payne (51) reported the results of treatment from 1937 to 1948 inclusive The absolute five year survival rate of all *new patients male and female treated and* untreated was 34 6 per cent All patients lost to follow-up were considered dead of the disease and treatment consisted of both radical mastectomy and/or radiotherapy The absolute ten year survival rate was 21 per cent The net five year survival (excluding those cases lost to follow-up and those having died of intercurrent disease) was 40 per cent

At the Mayo Clinic Harrington (23) has reported the results of surgical treatment of *unilateral breast cancer in women for the* period 1910 to 1946 inclusive Treatment consisted of radical mastectomy followed by radiotherapy in patients with malignant axillary nodes Follow up study was successful in 98 4 per cent of the patients, however those patients lost to follow up were dropped from the study and excluded from statistical analysis All patients known to have died were considered dead of the disease Only those patients treated by radical mastectomy were reviewed The survival rate is shown in table 34

TABLE 34

Verified Axillary Metastases	*Survival Rate (Per Cent)* 5 years post operatively	*Survival Rate (Per Cent)* 10 years post operatively
Present	32 5	18 0
Absent	78 3	61 2
Total	51 2	34 6

After Harrington (1952)

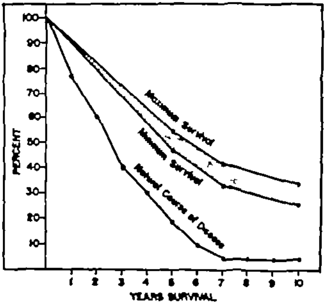

FIG 82 After Robnett Jones and Hazard (48) 1950

A quinquennial study during this period indicated a consistent and progressive improvement in survival obtained by radical mastectomy during the course of these many years Criteria of operability have always been quite lenient and a change in these criteria could hardly account for the appreciable increase in the survival rate Earlier diagnosis and more effective treatment must certainly play a responsible role

The recurrence and survival rates of 203 patients with cancer of the breast treated at the Cleveland Clinic have been reported by Robnett Jones and Hazard (48) In addition to showing survival data (fig 82) as a whole for each group in accord with Portmann's classification and pathologic type of tumor *these authors further subdivided their cases* to indicate survival rates according to treatment—surgery alone and surgery plus post operative X ray therapy In this series of 203 cases of breast cancer the over-all five-year survival was 47 7 per cent and the ten year survival was 26 7 per cent The extent of the disease (Portmann classification) was found to be the most important

index of survival. Pathologic type of tumor was found to be of secondary importance.

Local recurrence within the operative field occurred in 14.2 per cent of all patients and in 18.5 per cent of those patients followed for five years. The incidence of local recurrence was related to the degree of axillary lymph node involvement.

A review of breast cancer as treated in some of the medium sized and smaller communities of New York State from 1920 to 1947 has been presented by Burdick and Chanatry (6). In these communities the diagnostic and therapeutic facilities are not always of the same standard as in the urban cancer centers. However, the over-all end results compare favorably with the larger cities in the United States and abroad. Marred only by the fact that 28 per cent of the patients were lost to follow-up and thus considered dead of the disease, the over-all five year survival rate was 43 per cent, and the "cure" rate was 38 per cent. These figures are representative of general surgery in central New York State. In cases without axillary metastases the five-year "cure" rate was 51 per cent, and in cases with axillary metastases the five-year "cure" rate was only 26 per cent. The over-all ten year survival rate was 22 per cent, and the "cure" rate was 19 per cent.

Of 804 patients treated by radical mastectomy, 42 per cent were found to be alive and well at the end of five years. This result of surgical treatment compares favorably with similar studies in more specialized surgical clinics.

In discussing the results of radical mastectomy Halsted (18), in 1907, asserted that in the ultimate survival of the patient "the variety of the cancer, the time elapsed since its appearance, the degree of outlying involvement, the activity of the gland (lactation, age of the patient), the thoroughness of the operation, are important factors."

The results of radical operations for the cure of cancer of the breast at the Johns Hopkins Hospital were reported by Halsted in 1907. Excluding 65 patients in whom simple surgery was found more suitable, there remained 232 patients treated by radical mastectomy. In about one half the patients a supraclavicular neck dissection was combined with radical mastectomy. The end results in 18 patients were unknown, nevertheless, these untraced cases were computed as dead of the disease.

The three year survival rate was 38.3 per cent with a relative "cure" rate of 32.3 per cent. The five year survival rate (revised) was 28.9 per cent with a relative "cure" rate of 24 per cent.

Lewis and Rienhoff (31) in 1932 in a most exhaustive study reviewed a series of 950 consecutive breast cancer cases observed at the Johns Hopkins Hospital during the 42 year period 1889 to 1931. It is unfortunate but readily understandable that during this long time-lag in follow-up 22 per cent of the patients were completely untraced. Consequently, because of this and other factors, of an over-all total of 950 patients, accurate survival information was available in only 420 or 44.2 per cent. Considering only these 420 patients the five year survival following radical surgery was 18.1 per cent. At the time of the Lewis and Rienhoff report there were 97 patients living and well of whom 67 per cent had survived five years.

An analysis of the results of treatment at the Johns Hopkins Hospital for the 11 year period 1932 through 1942 was carefully reported by Jones (26). Beginning in 1932 there were 304 ward patients (private patients were not included in this study) admitted to the wards of the hospital during this period. Fifty-two (17 per cent) of these patients were considered unsuitable for radical mastectomy and were treated by radiotherapy with or without simple surgery.

There were 31 patients (12 per cent) lost to follow up

The over-all five year survival rate (excluding those patients lost to follow-up) was 34 per cent Considering all patients lost to follow up as having died of cancer the revised five year survival rate would then become 29.3 per cent, a figure almost identical with the earlier results of Halsted The five year survival rate for patients with negative axillary nodes by pathologic examination was 66 per cent whereas it was only 26 per cent in patients with positive axillary metastases

Lewison Trimble and Griffith (33) reviewed the latest results of treatment at the Johns Hopkins Hospital and reported the five and ten year survival rates for all patients treated by surgery during the period 1935 to 1940 inclusive (tables 35 and 36) Successful follow up was achieved in 94.5 per cent of 220 patients Radical mastectomy with or without radiotherapy was performed in 204 patients. Simple mastectomy was performed in 14 patients and local excision was performed in 2 patients (one patient refusing further surgery and the other having extensive pulmonary metas-

TABLE 35

Five Year End Results of Surgical Treatment for Breast Cancer (1935–40) at the Johns Hopkins Hospital

Type of Treatment	Stage of Disease	Number of Patients	Living and Well		Living with Recurrence		Total Survivors	
			No.	Per cent	No.	Per cent	No.	Per cent
Radical mastectomy	Breast alone	78	44	56 4	6	7 7	50	64 1
	Breast and axilla	126	35	27 7	5	4 0	40	31 7
Total		204	79	38 7	11	5 4	90	44 1
Simple mastectomy	Breast alone	5	2	40 0	—	—	2	40 0
	Breast and axilla	9	2	22 2	—		2	22 2
Total		14	4	28 6	—	—	4	28 6
Local excision	Breast alone	1	1	100	—	—	1	100
	Breast and axilla	1	—	—	—	—	0	0
Total		2	1	50	—	—	1	50
Total		220	84	38 2	11	5 0	95	43 2

TABLE 36

Ten Year End Results of Surgical Treatment for Breast Cancer (1935–40) at the Johns Hopkins Hospital

Stage of Disease	Number of Patients	Living and Well		Living with Recurrence		Total Survivors	
		No.	Per cent	No.	Per cent	No.	Per cent
Breast alone	84	34	40 5	6	7 1	40	47 6
Breast and axilla	136	23	16 9	1	0 7	24	17 6
Total	220	57	25 9	7	3 2	64	29 1

tases). All cases were verified by pathologic examination, and patients lost to follow-up or dead of intercurrent disease were considered as dead of cancer.

The five year survival rate for patients without axillary metastases by microscopic examination was 64 per cent, whereas the five year survival rate for patients with axillary metastases was only 31 per cent. A special review of 64 cases of breast cancer known to have survived ten years or longer failed to reveal any histological characteristics which could be correlated with a favorable prognosis or long time survival.

For all cases of breast cancer treated by surgery the five year survival rate was 43.2 per cent, whereas the five year "cure" rate was 38.2 per cent. The ten year survival rate was 29.1 per cent. These figures represent an improvement in end results of almost 15 per cent above the earliest Johns Hopkins Hospital survival statistics reported by Halsted almost fifty years ago.

Geschickter, in his excellent book entitled "Diseases of the Breast" (12), has analyzed the five year survival rate of 1,957 cases of breast cancer. It is presumed that some of this clinical material represents patients treated at the Johns Hopkins Hospital prior to 1942. This series included 75 patients in whom no treatment was given. The rate of successful follow-up was not stated. The over-all five year survival rate was 34.1 per cent. Patients without axillary metastases had a five year survival rate of 66 per cent, and patients with axillary metastases had a five year survival rate of 19 per cent.

In a comparative review of treatment in the American literature Geschickter found an average five year survival rate of 36.9 per cent. This clinical material represented a total of 8,585 cases of breast cancer reported by 13 different groups of surgeons. Patients without axillary metastases had a five year survival rate of 66.7 per cent, and patients with axillary metastases had a five year survival rate of 23 per cent.

A unique and particularly interesting study of 298 consecutive cases of breast cancer was reported by Finney, Merkel and Miller (10). All cases were the private patients of four exceptionally prominent and distinguished surgeons who received their training either directly or indirectly as disciples of Dr. William S. Halsted.

The 15 year period 1930 to 1945 was surveyed, and the diagnosis was confirmed by microscopic examination in every case. All patients were treated by radical mastectomy with supplementary radiotherapy being given to only 19 patients. Follow-up was exceedingly good, being successful in 280 patients (94 per cent). The operative mortality was low, three patients (one per cent) dying as the result of surgery.

The five year survival rate (calculated exclusive of those patients lost to follow-up and postoperative deaths) was 49 per cent. The ten year survival rate was 19 per cent. Correcting the over-all survival rate to include total patients treated there was a five year survival rate of 45.3 per cent and a ten year survival rate of only 17.4 per cent.

These statistics are indeed provocative but provide no ready answer to the unpredictable behavior of breast cancer. Why this similar group of patients, Baltimore's beau monde—operated upon by a quartet of Halsted's most skillful students—should have a *five year* survival rate which almost coincides identically with the present Johns Hopkins Hospital series yet have a *ten year* survival rate which is scarcely comparable remains a caprice of biostatistics. As suggested by Lees and Lees (30), data presented in a purely statistical fashion should not give the misleading impression of rigid mathematical certainty. "They should simply define with accuracy and with known

uncertainty what would otherwise have been more or less inaccurate impressions"

Conservative Surgery

In a candid but controversial study of the treatment of breast cancer by simple mastectomy combined with a high standard of radiotherapy, McWhirter (36) harks back to the suggestions of Bornk (4), Grace (14) Mitchiner Bailey and Price (39) Erskine (9) and many continental surgeons of this and an earlier day in what some critics call a pirouette of history repeating itself The contentions of McWhirter are based upon the obvious fact that the majority of cases of breast cancer are first seen when cancer is no longer confined to the breast alone With out exception there is universal accord that the results of radical mastectomy are ex cellent so long as the disease remains con fined to the breast, however as soon as the axilla becomes involved the results become considerably less favorable Therefore since surgical excision of the axilla is unnecessary when these regional nodes are innocent and radical mastectomy so often fails when these nodes are contaminated, McWhirter has advocated simple mastectomy followed by carefully planned radiotherapy in an ex tensive trial for patients with breast cancer This method of combined treatment is recommended as suitable for a large propor tion of the total number of patients who are routinely seen with breast cancer *Simple mastectomy alone (without radiotherapy) has not been designed or recomended to replace radical mastectomy*

Five main principles in the radiotherapy of breast cancer are emphasized

1 The axillary and supraclavicular nodes must be treated as one continuous chain

2 The internal mammary nodes must be treated in continuity with the chest wall

3 Hard quality radiation is essential

4 Adequate dosage must be delivered throughout the entire area of treatment

5 Only one course of treatment should be given

In Edinburgh the policy adopted has been to carry out only a very conservative simple mastectomy and to treat the axilla entirely by radiotherapy The results of all cases (1,345) referred from almost all of south and east Scotland between the years 1941 to 1945 are shown in table 37 The five year survival of all patients coming to the hospital (treated and untreated) was 43 7 per cent More recently, McWhirter has ana lyzed his cases for the period 1941 to 1947 inclusive (35a) to determine the over all five year survival rate For the ten year survival rate the results obtained in the period 1941 and 1942 have been analyzed Of the 1,882 cases recorded in the period 1941 to 1947, no operation was performed in 257 cases (14 per cent of the total) and unfortunately, there is no histological confirmation in 252 Almost all of this latter group without histological proof, however were cases of ad vanced disease and 235 of these cases were already dead or showed gross recurrence at the end of five years

Because of the outstanding zeal of one man with an excellent program of diligent follow-up McWhirter has been able to trace *all* patients Due to the difficulty in deter mining the exact cause of death, it was assumed that all deaths were due to breast cancer The absolute five-year survival rate was 42 per cent and the absolute ten year survival rate was 25 per cent (table 38)

There certainly appears to be no marked or significant difference between this chal lenging survival rate and the five year sur vival rate of superior surgical clinics else where 39 6 per cent (absolute survival rate) at Memorial Hospital 43.2 per cent (surgi cal survival rate) at the Johns Hopkins Hospital and 48 7 per cent (clinical cure'

TABLE 37

*A Review of All Patients with Breast Cancer (1,345) Observed by McWhirter (1941 to 1945)**

Operable, 60 Per Cent		Inoperable (Radical Operation), 40 per cent	
Axillary glands negative	Axillary glands positive	Advanced locally	Distant metastases
24 per cent	36 per cent	25 per cent	15 per cent
Axillary dissection unnecessary	Disputed group	Radical mastectomy contraindicated	Radical mastectomy contraindicated
Simple mastectomy + x-rays	Simple mastectomy + x-rays	Simple mastectomy + x-rays or x-rays alone	No treatment or palliative treatment
5 year survival rate, 89 per cent	5 year survival rate, 44 per cent		
All operable patients (757), 5 year survival rate, 62 per cent		All patients with locally advanced cancer (389), 5 year survival rate, 29 per cent	
All patients without evidence of distant metastases (1,146), 5 year survival rate, 50 5 per cent			
Every patient (treated and untreated) coming to the hospital (1,345), 5 year survival rate, 43 7 per cent			

* After McWhirter, 1950

TABLE 38

All Cases of Primary Breast Cancer Recorded

Stage of Disease	1941–47 5-Year Absolute Survival Rate			1941–42 10-Year Absolute Survival Rate		
	Total	No alive	% alive	Total	No alive	% alive
Operable	1063	612	58	254	99	39
Locally Advanced	546	162	30	157	23	15
Distant Metastases Present	273	12	4	69	0	0
Total	1882	786	42	480	122	25

After McWhirter (351) 1954

rate) at Presbyterian Hospital Careful study of McWhirter's statistics indicates (assuming his "operable" cases to be comparable to Stage I and Stage II) a five year survival rate of 62 per cent, and a five year survival rate of 50 5 per cent if one includes all cases without evidence of distant metastases

Although the prejudices of doubt are often difficult to dissipate, it is clearly evident that the five year survival rates reported by McWhirter are equal to any achieved by the accepted procedure of a classic Halsted radical mastectomy, with or without radiotherapy It is, of course, also quite obvious that the principles of McWhirter are not merely simple mastectomy and intensive radiotherapy Special techniques are employed both at operation an
administration of X-ray thera

If one could reduce the ma
diagnostic error to an absol
then all Stage I cases of breas
be safely and successfully trea

mastectomy However, the thorns of experience have taught us that diagnostic errors based upon physical examination alone may vary between 25 and 50 per cent Thus the hazards of planning a treatment policy based upon the diagnostic evidence of clinical staging are evident

The success of the McWhirter technique lies primarily in the very early and late cases of breast cancer In the broad middle-ground of borderline cases with less extensive axillary involvement confidence in well planned radical surgery of the axilla must merit our continued trust Regardless of McWhirter's most gratifying survival statistics skeptics and sound surgeons as well still believe the surest and safest method of eradicating axillary metastases is by radical surgical excision Time alone will tell And when the ten year survival rate is confirmed by other investigators perhaps the added "years teach much which the days never know However in the early light of McWhirter's statistics the logic of radical mastectomy may rest upon reasons which reason alone finds difficult to define By this renaissance of an idea which had long since lapsed into the limbo of the past McWhirter challenges our current complacency Future experience alone must be the immutable standard and impartial judge of the merit of this conservative method of treatment

An excellent evaluation of the treatment of cancer of the breast at the University of Edinburgh has been prepared by Ackerman (60) who was privileged to review the clinical records and pathologic material of McWhirter at the Royal Infirmary Of 719 consecutive patients with breast cancer there were only thirteen patients in whom the pathologic diagnosis was in question or found to be in error The therapeutic technique of McWhirter was complicated in 220 patients by the ancillary procedures of ovarian sterilization hormone therapy and local excisional surgery However it is to be remembered that similar series of breast cancer cases treated by more conventional means are also complicated by these very same factors

The local persistence of cancer in the group of cases considered operable was higher than might be expected The actual incidence of local recurrence or persistence in those cases which failed to survive five years was unknown

There was a considerable morbidity associated with McWhirter s technique of radiotherapy Despite the most meticulous precautions there were 47 patients with severe radiation changes including three requiring amputation of the arm

In the opinion of the present author, McWhirter's thesis that simple mastectomy and X ray therapy is the treatment of choice in cancer of the breast is not proven However it is evident that this technique does produce five year *survival* rates which are comparable to conventional types of therapy This appears to be true despite the fact that

a An extremely conservative simple mastectomy which is recommended is theoretically unsound and unsafe in that it probably cuts across the invisible perimeter of tumor permeation and

b There is no histologic proof of sterilization by radiotherapy of the regional nodes

Ackerman notes that despite a favorable five year absolute survival rate many of the patients are *not* cured Certainly the use of simple mastectomy alone without the benefit of superior or well planned radiotherapy is to be condemned as a tragic surgical shortcut This, of course is *not* the intention of McWhirter

The McWhirter technique permits persistent and residual carcinoma cells to remain viable and apparently intact within the

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If one could reduce the margin of clinical diagnostic error to an absolute minimum, then all Stage I cases of breast cancer could be safely and successfully treated by simple

mastectomy However the thorns of experience have taught us that diagnostic errors based upon physical examination alone may vary between 25 and 50 per cent Thus, the hazards of planning a treatment policy based upon the diagnostic evidence of clinical staging are evident

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Ackerman notes that despite a favorable five year absolute survival rate many of the patients are *not* cured Certainly the use of simple mastectomy alone without the benefit of superior or well planned radiotherapy is to be condemned as a tragic surgical short cut This of course is *not* the intention of McWhirter

The McWhirter technique permits persistent and residual carcinoma cells to remain viable and apparently intact within the

operative area. This region and its adjacent axilla is rich in blood supply and profusely endowed with lymphatics. Leaving this malignant residue behind is certainly not the safest and surest method of eradicating this disease.

Keynes (27), a staunch advocate of conservative surgery and radiotherapy, observes that "orthodoxy has been greatly shocked by this subversive tendency—but history cannot be denied." Unfurled prophecy, however, must not be confused either with history or destiny.

Sir Heneage Ogilvie (42) has published the final pages of a diary which he kept during a visit to America in 1937. The kaleidoscopic and heterodox Sir Heneage had this to say concerning the orthodox Halsted tradition. "I watched several dyed-in-the-wool Halstedians performing the radical amputation of the breast, and I felt that here the knife ideal, carried to its extreme, is the 'letter that killeth.' A dissection of the axilla with the knife is distressing to watch, the surgeon takes more than an hour to do part of the operation for which we should need ten minutes. . . ."

Extended Radical Mastectomy, Ultra-Radical Surgery

W. Sampson Handley (22) was one of the first to call attention to the frequency of internal mammary lymph node metastases in breast cancer, and he advocated the parasternal insertion of radium as an additional prophylactic procedure against the further spread of cancer cells. The results of radium implantation were not encouraging. This procedure has its technical difficulties of application, and the intensity of radiation was without uniformity along the entire internal mammary lymph node chain.

By being the most vigorous champion of the lymphatic permeation theory of breast cancer dissemination, Handley seems to have added important evidence to the rationale of radical mastectomy. The logic of Handley's operation for breast cancer centered upon the complete removal (en masse) of the primary tumor and all of the permeated lymphatics (except the internal mammary nodes) in the area including the regional lymph nodes. The exploration of the anterior mediastinum and removal of the internal mammary nodes was performed but only in special cases. This discerning surgeon was also one of the first to note that the curative and reparative processes of nature, although inadequate to effect a cancer cure, are a normal part of the cancer process. This early appreciation of host resistance added hope to the therapeutic horizon.

The excellent work of Richard S. Handley (19) (see Chapter II) has recently extended the brilliant and original investigations of his eminent father. In a series of 119 patients with operable breast cancer Handley biopsied the internal mammary lymph nodes as a sort of "pathologic reconnaissance." In 34 per cent of these cases metastases had already invaded the internal mammary chain of nodes, and presumably radical mastectomy in these cases was doomed before it was begun. In discussing the practical implications of these findings the speculations of Handley are particularly pertinent. Readily admitting that the axillary lymphatic pathways are the main drainage channel of the breast, Handley contends:

"The case is far otherwise with the internal mammary chain. It lies on the pleura and is a main lymphatic road from the liver and diaphragm. It is very difficult to reach surgically, yet is often heavily implicated. Not only do I think that spread of carcinoma to the internal mammary chain accounts for those puzzling recurrences which occur when a radical mastectomy has been done on an early case, but I also believe that it accounts for the fact that metastasis is commonest in

the lungs and pleura and that, in post mortem series the liver is the second most commonly invaded organ I think in fact, that in breast carcinoma the internal mammary chain is the principle highway of death

In the light of these important findings a small group of surgeons have renewed their efforts to increase the scope of the classic Halsted radical mastectomy (see Chapter XII) Among these champions of extended or super radical mastectomy Wangensteen has noted that approximately 60 per cent of patients having cancer of the breast with axillary involvement have evidence of the disease beyond the reach of the conventional radical mastectomy These metastases have been noted in the internal mammary chain of lymph nodes in the mediastinal lymph nodes and in the supraclavicular region By means of a cervicothoracic approach and median sternotomy the classic radical mastectomy has been extended by Wangensteen to include a supraclavicular dissection an upper mediastinal dissection and removal of the internal mammary chain of lymph nodes. The operative mortality and morbidity associated with this type of heroic surgery remain to be defined in a large enough series, whereas survival must await the test of time

Wangensteen (57) who is a distinguished surgeon and careful critic states 'Today it should be said I believe the Halsted operation for cancer of the breast is outmoded it is not radical enough it is an incomplete operation for cancer of the breast in patients exhibiting axillary metastases' However there are those who believe that the strength of this condemnation and criticism does not lie in the weakness of the thing criticised For to criticize this operation is certainly easier than to improve it It remains to be seen whether such strategic surgery as super radical mastectomy can more successfully cope with breast cancer which has perhaps spread to the internal mammary nodes on the same side and probably beyond

Lewis (30a) reporting the preliminary results of the extended or super radical mastectomy from Wangensteen's clinic, states that 'radical mastectomy is an operation that requires amendment In its traditional form it fails to cure many so-called operable cases of cancer As generally used today it is an incomplete operation limited by two anatomical barriers the clavicle and the bony chest wall Wangensteen has added to the classic Halsted operation both a supraclavicular and mediastinal dissection

Certain assumptions are implicit in attempting so extensive an operation as super radical mastectomy It must be considered possible in the first place to obtain a long term survival in a sufficiently large number of cases even after breast cancer has spread to the regional nodes Also, lymphatic involvement of the regional nodes if not in a consecutive manner then at least in a progressive manner must be assumed to be the predominant mode of metastatic spread Alternate routes of spread not amenable to this type of surgical excision must be considered as unlikely areas of dissemination of breast cancer

This type of heroic surgery is certainly not indicated for all cases of breast cancer Lewis believes that the super radical operation is primarily indicated for those patients who have unequivocal evidence of axillary metastases at the time of radical mastectomy In a series of 50 patients treated by super radical mastectomy Lewis reported that 30 (60 per cent) had cancer which had spread beyond the confines of the conventional radical dissection This is not surprising since the initial selection of patients specifically chosen for this procedure was based upon an advanced disease How

doubtful whether these innovations will be the certain cure or the sovereign remedy. Refinements in the technique of radical mastectomy or super-radical mastectomy even when done promptly, meticulously and with the utmost of skill can hardly be the ultimate answer. The anatomical limit of free franchise among competent surgeons remains to be expediently defined. Time alone will properly evaluate the place of conservative or ultra-radical breast surgery, but until then they should be cautiously undertaken as a clinico-experimental exercise and performed in a spirit of hopeful consideration—for "when desperate ills demand a cure, distrust is cowardice and prudence a folly." The urgent need for an effective cancer chemotherapeutic agent, a selective cell poison, a specific target cell nucleo-toxin, an anti-metabolite against cancer, an adjunct to host resistance, a tumor inhibiting steroid or anti-viral antibiotic, can best be measured by today's appalling toll of cancer of the breast.

The glorious goal in the "cure" of breast cancer is the removal of the primary tumor with *all* of its areas of lymph drainage. This, of course, must be done before the disease has disseminated (by both blood and lymph channels) beyond the scope of surgery. It is a matter of the greatest importance to determine the limitations wherein the increased salvage of extended radical mastectomy is offset by the law of diminishing returns (increased operative mortality, morbidity and postoperative disability). The interception of such crucial avenues of death as blood-borne metastases, mediastinal, pleural, lung, liver, supraclavicular and contra-lateral axillary and opposite internal mammary lymph node metastases remains without serious interdiction despite the strategy of super-radical surgery.

Current concepts of breast cancer are constantly changing. The idea of a single focus of malignant growth is gradually giving way before the theory of multicentric origin. The prophecy of recent experience throws new light on the curious pattern of breast cancer behavior during pregnancy, at the menopause, following castration, during the administration of the sex steroids, and subsequent to hypophysectomy and adrenal ablation. The concept of the complete autonomy of the breast cancer cell is no longer sacred when even the subtle influence of an upset hormone homeostasis can modify the course of mammary malignancy. The perplexing pattern of the distribution of metastases, frequent in the bones of the spine and pelvis yet infrequent in the bones below the knee or elbow, common in the visceral organs (except spleen) yet uncommon in the skeletal muscle, remains an oft observed but imperfectly explained phenomenon based upon the random distribution of metastases by mechanical circulatory factors of hemodynamics. Observation and logic are said to be the beacons of wisdom, yet science is still seeking the secret of long-term quiescence—a nidus of breast cancer cells lying dormant for 20, 30 or even 40 years before becoming a fulminating harbinger of death. Why are the results of radical treatment in advanced breast cancer so much worse than simple surgery, X-ray therapy, hormone therapy or even no treatment at all? What are the basic principles of stromal-tumor-host relationships?

It is, of course, obvious that there are many problems relating to the surgical treatment of breast cancer which have yet to be solved. In an excellent evaluation of this subject Orr (43) reminds us that "to champion one method of treatment or technique of operation to the exclusion of all others may smack of dogmatism, and dogmatism never does much toward the solving of scientific problems." We must keep an open and discriminating mind concerning the

many opinions extant and look with a discerning eye upon future conclusions which may lack basic truths. Opinions should be respected but should not be mistaken for facts."

The ancient Roman Seneca once said, 'Our forefathers have done much but they have not finished anything' We of the present ephemeron must carry "from the altar of the past the fire and not the ashes', for the doctrines of surgery do not expire with each succeeding generation of surgeons

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CHAPTER XI

The Surgical Treatment of Breast Cancer

Radical Mastectomy

Radical mastectomy has been practiced by many surgeons for over half a century and is considered by most to be the operation of choice in the surgical treatment of cancer of the breast Yet it is evident to all that there are many problems pertaining to breast cancer and the technique of its surgical treatment which remain unsolved In surgery, "the greatest of faults is to be conscious of none" Velpeau (63), in 1856, censorious of his own shortcomings, noted with keen disappointment "To destroy a cancerous tumor by surgical means is usually an easy matter, and but little dangerous in itself, but the question arises, whether such a proceeding affords a chance of radically curing the patient This proposition is still undecided although it has been discussed since the time of Hippocrates"

Today, despite a voluminous surgical and medical literature, our salient facts are still too few and our unsatisfactory results are still too many What is considered therapeutic orthodoxy in one clinic is often regarded as therapeutic heterodoxy in another It is necessary that we arrange our factual information into definitive concepts of therapy *It is important to impart this ever-growing knowledge to all surgeons and physicians in whose power it is to use it wisely and most effectively* Although Martin Fischer pointed out that, "the printed page is not the truth nailed down, but the author," *there is much merit in knowing what to do and when*

Progress in surgical therapy is forever here *It is a serious error to regard the operative treatment of breast cancer as having been cast in a mold* Radical mastectomy is a satisfactory present-day standard which undoubtedly will be modified, combined with ancillary therapeutic agents and improved by degrees in the future Predominant surgical *opinion currently favors radical mastectomy* Its precedent has established both a pattern and a principle in the operative treatment of breast cancer This is true despite current clinical experiments with 1) simple mastectomy and radiotherapy and 2) *extended radical mastectomy for the excision* of the internal mammary chain of lymph nodes

We urgently need a simple scientific basis for determining the best possible treatment for each individual patient As suggested by Smithers et al (58) in regard to varying modes of treatment. "We should not be concerned with advocating one, but in making the best use of all By using each to its best advantage and by making all methods—in combination when needed—available to all patients, we might improve the results still further "

However, there is great difficulty in deciding upon the best treatment policy for each patient The extent of the disease is so often undiscoverable or unrecognized, and the biologic behavior of both the tumor and *the host is equally unpredictable* There is good evidence at present to suggest that both

surgery and radiotherapy can be effective in the control of cancer but surgery is more effective when the disease is localized to the breast or has not extended beyond the axillary nodes. However, the surgical problem of metastases to the internal mammary nodes remains as yet unanswered Thus, given a patient with operable breast cancer, with or without clinical evidence of axillary metastases radical mastectomy is the treatment of choice and should be performed as promptly as possible

Criteria of Inoperability

In the selection of patients for radical mastectomy certain criteria of inoperability are not only desirable but essential as guides to definitive surgery These invaluable standards are drawn from the errors of past experience With the passing of years, sound surgical judgment has found that in the selection of patients for radical mastectomy if the beginning is bad the ending is worse More lives are probably shortened by poor selection than by poor surgery It has been a common but tragic experience to discover that the results of surgery are most unfavorable when radical mastectomy is performed in desperation on patients with advanced breast cancer Many years ago Deaver and MacFarland noted that the apparent disrepute of radical mastectomy was due, in a large measure to the willingness on the part of surgeons to accept hopelessly advanced cases for radical operation.

Thus, disciplined by experience criteria of inoperability have been formulated based upon standards of physical examination and clinical group-staging The fallibility of this evaluation is an ever present possibility and an accepted calculated risk. However in a patient with a large fixed fungating tumor, or one encased with carcinoma en cuirasse or where there are firm, fixed regional nodes in which metastases have undoubtedly

Table 39
Criteria of Inoperability

(a) When the primary growth has become attached to the bony thorax
(b) In the presence of cancer en cuirasse or of subcutaneous nodules or skin infiltration situated more than two inches from the primary growth
(c) If there is a fixed mass of growth in the axilla evidently adherent to its walls
(d) If there is marked edema of the arm
(e) If the supraclavicular nodes are enlarged hard and fixed
(f) If there is evidence of visceral or bone metastases
(g) If there is incurable constitutional disease tuberculosis or diabetes for example likely to be fatal in a few years at most or to lead to a postoperative fatality
(h) In the acute forms of carcinoma

After W Sampson Handley (23) 1906

passed through the shadow of the valley of the axilla, radical surgery certainly should be withheld in favor of conservatism Every effort must be made in these patients not to undo the body s existing defenses for confining the growth

A classification of the positive contraindications for radical mastectomy in breast cancer was suggested early in the modern era of breast surgery by W Sampson Handley (23) (table 39) Today criteria of inoperability are widely varied There is a great diversity of opinion among surgeons on this subject surpassing any set of rules or standards. An eager and enthusiastic young surgeon may rashly challenge the forbidden barrier of this frontier, but alas, they make a glorious shipwreck who are lost in seeking worlds' beyond their reach

Adair (2) endorses the simple rule of considering any case operable in which the disease is localized in the breast or the breast and axilla and in which we consider there is a chance of cure no matter how small that chance Radical mastectomy is not per

formed in the presence of supraclavicular metastases, distant metastases or inflammatory carcinoma At the Memorial Hospital in New York, Adair has interpreted the standards of operability along very generous and lenient lines Since there is no other therapeutic agent to be regarded as "curative," "we would prefer to perform ten radical mastectomies in unfavorable cases than neglect to do the radical in one in which we might be mistaken as to prognosis"

At the Mayo Clinic, Harrington (25) in a study of 8,074 women with unilateral breast cancer, found it difficult to make a sharp distinction between operable and inoperable lesions Any tumor of the breast was considered operable by radical mastectomy if it was freely movable on the chest wall, regardless of ulceration or the presence (in some cases) of satellite cutaneous nodules Patients were also accepted for operation if they had a diffuse type of malignancy or developed breast cancer during pregnancy or lactation Criteria of inoperability consisted of large tumors fixed to the chest wall, extensive metastases to the axillary or supraclavicular nodes and distant metastases Harrington has "accepted for operation all patients to whom I felt there was a reasonable chance of offering comfort or longer life, as well as those for whom I felt there was a reasonable chance of cure It may seem that these rules of operability have not been drawn strictly enough and that patients who had too extensive growths have been accepted for operation This is a matter of opinion, however, and justification has been found in many cases in which the condition was thought to be hopeless before operation but the patients lived to enjoy years of comfort"

The discrepancy between technical operability and clinical "curability", however, has been resolved by many surgeons for practical purposes by careful adherence to specific criteria in the selection of patients Following a critical review of the cases of breast cancer treated at the Presbyterian Hospital in New York, Haagensen and Stout (20, 35) came to the conclusion that radical mastectomy was contraindicated in certain cases of advanced breast cancer despite the feasibility of the technical performance of this operation At about the same time (1943), Portmann, in a symposium on cancer of the breast (unpublished), presented similar criteria of incurability

As noted by Haagensen and his colleagues, radical mastectomy was an important therapeutic procedure which had been used at times indiscriminately in patients whose disease was well beyond the scope of radical surgery In seeking more precise clinical criteria, Haagensen selected standards which would permit only those patients with some chance of "cure" to undergo radical mastectomy The original "criteria of operability" which were published in 1943 were based upon a clinical examination of the tumor locally and clinical evidence of regional extension Except for the category of pregnancy and lactation these criteria have been valuable and generally accepted by many surgeons as a therapeutic guide In appraising these standards, Haagensen readily recognized the fallibility of clinical examination and the "lack of a reliable method for determining the existence of regional lymph node metastases" Certainly another possible pitfall is the unique and unpredictable biological behavior of an exceptional case of breast cancer designated as "categorically inoperable" For instance, Meyer, Dockerty and Harrington (42) at the Mayo Clinic reviewed seventy-four cases of inflammatory breast cancer treated by radical mastectomy and found that three cases survived five years and one case survived nine years

By resorting to a new method of multiple

biopsy—substituting pathologic evidence for clinical evidence of regional lymph node metastases—Haagensen recently has modified his initially proposed criteria of operability (table 40) The technique of triple biopsy (tumor, supraclavicular lymph nodes and internal mammary lymph nodes) "has increased the exactitude of our criteria of operability for the disease and has avoided much futile surgery" This formidable technique of triple biopsy may also be of value in selecting specific patients for super radical mastectomy which includes the block dissection of the internal mammary lymph node chain

In a critical analysis of recurrent breast cancer, Shimkin and his colleagues (50) found during a long period of study, a small group of 28 patients with recurrent breast cancer who were inadequately operated upon elsewhere Subsequently, these patients underwent radical mastectomy at the University of California Hospital, and their five year survival was surprisingly good—57 per cent. These selected cases must certainly represent a group of biologically indolent tumors which remained localized for a sufficient period of time to be regarded as clinically operable after a considerable period of time The slow growth and delayed spread of these tumors is emphasized by the fact that at reoperation the axilla was still free of metastases in three patients Although survival is surely determined in part by surgical selection based upon standards of operability yet as noted by Shimkin et al, this series of cases reflects the important role of biological behavior and host resistance *Prolonged survival is quite possible in an occasional case of a slow-growing tumor which may reach a considerable size* With enlarged regional nodes and fixation these cases are considered categorically inoperable for radical mastectomy However, survival for a long period of time under any circumstances would have probably taken place, and an equally favorable result could be expected if treated by simple surgery and radiotherapy

TABLE 40

Breast Carcinoma Is Inoperable

1 When extensive edema of the skin over the breast (more than one third of the skin area) is present
2 When satellite nodules are present in the skin over the breast
3 When the carcinoma is the inflammatory type
4 When any two or more of the following signs of locally advanced carcinoma are present
   a Ulceration of the skin
   b Edema of the skin of limited extent (less than one third of the skin over the breast)
   c Fixation of the tumor to the chest wall
   d Axillary lymph nodes measuring 2.5 cm or more in transverse diameter
   e Fixation of axillary lymph nodes to the skin or the deep structures of the axilla
5 When there is edema of the arm
6 When in patients with clinically involved axillary lymph nodes a supraclavicular dissection reveals metastasis in the supraclavicular lymph nodes
7 When in patients with clinically involved axillary lymph nodes biopsy of the internal mammary lymph nodes reveals metastasis
8 When roentgenographic study of the skeleton reveals metastases or when the patient has a history of recently developing pain in the back or pelvic region suggesting metastases
9 When roentgenographic study of the lungs reveals metastases
10 When palpation of the liver suggests that it contains metastases

After McDonald Haagensen and Stout (35) 1953

Tomlinson and Eckert (60) carefully applied the original Haagensen criteria of inoperability to a group of patients who had been previously operated upon and routinely followed for breast cancer There were 107 patients in their group who by definition only were considered categorically inoperable yet 100 of these patients were treated

by radical surgery. The five year survival rate in this latter group was only two per cent, and both of these patients were classified in the category of pregnancy associated with breast cancer. The average survival time of these "inoperable" yet operated upon patients was only 36.3 months. The authors confirm the validity of careful selection of patients for radical surgery.

It is of paramount importance to determine whether or not strict standards of inoperability are justifiable in patients who are considered to be technically operable. *Surgical experience based upon survival and curability statistics attest to the validity of such criteria of inoperability.*

Clinical signs and symptoms are not always indicative or conclusive of the extent of the disease. Yet with a full sense of realization that criteria of inoperability for radical mastectomy depend upon clinical staging (which is subject to the error inherent in the human equation), the following standards are recommended as guides to definitive surgery. They are to be regarded as flexible and tempered by compassionate clinical judgment. Formulated to provide the best possible prognosis, they should not be ignored for esthetic or inconsequential reasons. Many years ago, Deaver, an eminently skillful surgeon, and McFarland (16) said, "any operation, the purpose of which is merely to remove as much malignant tissue as possible, or in cases where complete removal is out of the question, should be strongly condemned. Operations of this type contribute nothing to the comfort of the patient nor prolongation of life, on the contrary, the end is frequently hastened by exciting the disease to more active growth."

Contraindications to Radical Mastectomy

I. Inflammatory breast cancer.
II. Extensive edema of the skin associated with a diffuse and advanced disease.
III. Ulceration of the skin associated with a large and extensive cancer of the breast.
IV. Fixation of the tumor to the chest wall indicating muscle invasiveness.
V. Large or multiple axillary nodes fixed to the skin or surrounding structures.
   A. Persistent edema of the arm secondary to enlarged axillary nodes.
VI. The presence of carcinoma en cuirasse or multiple lenticular satellite skin nodules.
VII. Supraclavicular, contralateral axillary or visceral metastases confirmed by biopsy whenever possible.
   A. Clinical diagnosis of liver metastases considered acceptable.
VIII. X-ray evidence of pulmonary or skeletal metastases.
IX. Back pain or pelvic pain strongly suggesting osseous metastases which are not yet discernable by X-ray examination. Frequent re-examination required.
X. Advanced age, debility, or systemic disease precluding the advisability of major surgery.

In applying these criteria of inoperability one must be particularly critical and cautious in evaluating X-ray evidence based upon *solitary* lesions in either the lung or skeletal system. These may be coincidental findings which can be mistaken for metastases. I have recently had occasion to see a patient with breast cancer who had severe back pain which radiated to the hip and down the leg. The X-ray examination was *interpreted* as "a single osteoblastic metastasis" in the lumbar spine. Careful follow-up study revealed that the low back and leg pain was the result of a retrodisplaced uterus and the "single osteoblastic *metastasis*" which remained unchanged by X-ray examination was presumably a bone island or some similar

benign sclerotic osseous condition. An aspiration bone-marrow biopsy might have been considered of significant diagnostic assistance. However, this diagnostic aid is of importance only if positive.

Similarly, back or pelvic pain without demonstrable X-ray evidence of disease requires frequent re-examination often in conjunction with serum alkaline phosphatase and urinary calcium studies. The use of calcium excretion as a measure of osteolytic tumor growth has been described by Laszlo (28) and by Pearson, West, Hollander and Treves (50).

The problem of radical mastectomy for bilateral breast cancer occurring simultaneously depends upon a difficult differential diagnosis. If the bilateral disease appears to be the result of extension or metastasis, then conservative therapy is indicated. However, if the bilateral breast cancer appears to be the result of two foci of primary multicentric origin, then bilateral radical mastectomy may be the treatment of choice.

Patients considered categorically inoperable for radical mastectomy may be, of course, candidates for simple mastectomy and radiotherapy (see Chapter XV). Also if radiotherapy or hormone therapy is administered to patients considered inoperable (but without evidence of distant metastases), the primary lesion and the regional nodes may be found to regress markedly. Under these favorable circumstances there is a strong temptation to re-evaluate the patient and resort to radical mastectomy. However, microscopic evidence reveals that neither radiotherapy nor hormone therapy are cancerocidal or cause the disease to disappear totally, and that viable appearing cancer cells still remain within the breast and regional nodes despite clinical improvement. *Successful radiotherapy or hormone therapy does not render inoperable breast cancer subsequently amenable to surgical "cure" by means of radical mastectomy.* However, palliative surgery by means of simple mastectomy may now become an effective therapeutic adjunct.

As noted in Chapter VIII, clinical stage-grouping of breast cancer is desirable not only for the purpose of a more precise comparison of different series of cases, but also for a simplified classification of operability. Patients clinically grouped as Stage I or Stage II or primary site I or primary site II with metastases I are generally considered operable and acceptable for radical mastectomy.

Operability Rate

During the course of recent years the operability rate for radical mastectomy has been subject to the influence of two counteracting tendencies. The first and most important has been the progressive increase in operability due to the earlier detection, diagnosis and treatment of breast cancer. Adair found that only 22.6 per cent of breast cancer cases at the Memorial Hospital were operable in 1920, whereas in 1951 the operability rate had increased remarkably to 80.3 per cent. Cancer education and breast self-examination favor the early discovery and prompt treatment of patients with operable breast tumors.

On the other hand, a progressive increase in the acceptance and validity of criteria of inoperability has tended to lower the rate of operability. The refinement and improvement of radiotherapy and the development of palliative hormone therapy has increased the justification for conservative therapy in the borderline, poor risk or categorically inoperable patient.

Offsetting these tendencies, improved methods of anesthesia, operative technique, use of transfusions and antibiotics and the preoperative preparation of patients have permitted safer operations on the poor risk and elderly patients with breast cancer.

Thus the over-all operability rate during

the last 50 years at the Massachusetts General Hospital has varied only slightly from 72 per cent to 80 per cent of all primary cases admitted to the hospital The operability rate for radical mastectomy in most clinics throughout the country appears to be within a similar 75 per cent average range Accurate statistics on this point are difficult to standardize or verify due to the unknown number of patients with advanced disease who must never reach an in-patient status within the hospital McNealy has indicated that at the Cook County Hospital in Chicago, a large hospital for the care of the medically indigent, only 15 per cent of breast cancer cases could be considered clinically in Stage I when first observed

In a study of breast cancer cases examined at the Radiumhemmet between 1936 and 1941 inclusive, Nohrman (46) noted that the operability rate remained practically constant (81 per cent) despite the fact that the total number of cases increased annually Despite strict criteria of operability Haagensen reported an operability rate for radical mastectomy of 74 per cent.

In a long-term follow-up survey of all patients with primary breast cancer admitted to the Johns Hopkins Hospital from 1935 to 1940, Lewison, Trimble and Griffith (32) found that 80 per cent were considered operable for radical mastectomy However, it must be carefully noted that an indeterminate number of patients with advanced breast cancer were probably screened in the out-patient department or in their private physician's office where they were advised against entering the hospital for definitive surgery These patients with categorically inoperable breast cancer at the time they are first seen are seldom included in the statistics of over-all operability rates

Operative Mortality

There is ample reason to believe and every evidence to indicate that the operative mortality associated with radical breast surgery should be minimal. The collected figures, over a long period of time, of a large number of well qualified British surgeons revealed an average operative mortality of 1 65 per cent for radical mastectomy Riddell (52), in a personal series of 170 consecutive radical breast operations, reported that none of the patients died while in the hospital or within one month after operation In a careful study of this particular subject, Cole (12) found that the operative mortality rate in 122 cases of breast cancer under the age of 60 was 0 per cent and an identical 0 per cent rate was found in 67 cases of breast cancer operated upon over the age of 60 Thus, contrary to expectations, in the experience of at least this university hospital, the operative mortality apparently showed no significant difference between the young and the old An operative mortality of 0 85 per cent, regardless of age, was reported by Bell (7) in a large general hospital treating both private and clinic patients Haagensen, in a critical analysis, noted an operative mortality of 1 8 per cent. The definition of what is meant specifically by "operative mortality" in the matter of time relationships and postoperative complications must be clearly stated in interpreting this kind of biostatistical data

Radical mastectomy, with or without excision of the parasternal nodes, when skillfully performed with modern operating room facilities and with proper selection of cases should result in a low operative mortality. The adjuncts of good anesthesia, antibiotics and blood and fluid replacement should favor an approximate over-all operative mortality for the conventional radical mastectomy of not more than two per cent However, in less competent or inexperienced hands, postoperative deaths in any operation of the magnitude of radical mastectomy may be as high as five per cent or more

The most common causes of postoperative

death have been attributed to surgical shock, cardiovascular complications, infection and pulmonary problems including pulmonary embolism Yet despite the time required for this extensive and meticulous operative procedure, a careful surgeon should complete the radical dissection without the intervention of clinical shock in from three to four hours. Good surgical technique requires haste, but negligence is often the result of hurry

Precautionary measures include the preliminary insertion of an intravenous needle in either the arm or the terminal segment of the greater saphenous vein in the leg for the administration of blood, fluids or intravenous medication More recently, it has been our practice to use an arm vein in preference to a leg vein. This lessens the likelihood of venous thrombosis and prevents vein damage due to intravenous anesthesia. It is far safer to provide for this requirement prophylactically than to encounter the difficulties of a collapsed vein when blood or fluid replacement may be urgently needed in an emergency

Careful hemostasis, gentleness in the handling of tissues, rigid aseptic technique and the restricted exposure of denuded areas by covering the chest wall and skin flaps with warm saline compresses all aid in the prevention of serious surgical shock. Nothing exceeds gentleness and hemostasis in the prevention of shock. Speed is a factor of much lesser importance and shoud never compromise the careful dissection and gentle handling of tissues, which are so vital to the basic principles of radical mastectomy In addition to the avoidance of undue exposure and to maintaining the fluid balance, other factors to be considered in the prevention of shock are that the anesthesia need not be deep and the skin flaps in closure should not be drawn excessively tight across the chest wall In handling and transporting the patient gentleness should be the byword of nurse and orderly alike with particular and caution devoted toward the suppo the flail arm on the recently operated

GENERAL PREOPERATIVE MEASURE

Among the many factors responsible lowering of the operative mortality in ra breast surgery, perhaps the most impo single factor has been a better appreci of surgical physiology Operations of magnitude place a severe burden upo patients but particularly those who ma classified as poor surgical risks Perhap most serious of all deficiencies constitut poor surgical risk is caused by malnutr and anemia. Dehydration and electr imbalance are likewise of major import Myocardial disease recent coronary th bosis and cardiac decompensation are serious threat to survival following ra breast surgery However patients compensated heart disease or a coro thrombosis which occurred three to months prior to operation will usually t ate operation reasonably well.

Elderly patients tolerate radical ma tomy better than might be expected pr ing that complications are promptly r nized and effectively treated Alth cortisone and ACTH have been helpf improving operability, its use in pat with breast cancer must await a b understanding of its effect upon the m nant process.

The average age of most patients breast cancer who are operated upon this disease is between 50 and 60 The good reason, therefore to regard ra mastectomy during this age range w certain amount of prudent care and tional caution The elasticity of one s art and arterioles is no longer as flexib earlier in life. Vascular shock inciden blood loss and changes in the renal ve make older patients more likely to dev serious postoperative complications

The ill effects of hypoxia and anoxia are particularly disturbing in geriatric surgery. For this reason, anesthesia in patients undergoing prolonged operative procedures is a matter of the utmost importance. Exposure to heat or cold is poorly tolerated and is to be avoided.

Elderly patients are still susceptible to serious respiratory infection despite the advent of antibiotic therapy. Because of these well-known physiologic impairments incident to age, it is to be expected that some patients will have a lower reserve to support them during the stress and strain of major surgery. Thus, effective preoperative measures are more important in elderly than in young patients. Deficiencies, both nutritional and electrolyte, should be corrected and a thorough examination must be performed in all preoperative patients despite the serious nature of the malignant disease. Every surgeon must be vigilant and endowed with a high index of suspicion.

X-Ray Studies

Apart from the routine general work-up in which a patient's status is surgically evaluated with a view to the extent of the primary tumor and its contemplated technical removal, certain laboratory and X-ray studies are desirable and considered standard practice. An X-ray examination of the chest (anterior-posterior and lateral views are preferred) is routinely performed before operation. The films are brought to the operating room where they are re-examined prior to undertaking surgery. An asymptomatic pleural effusion or metastatic pulmonary disease may be discovered unexpectedly in patients who have what appears to be a small and presumably operable tumor. Repeated X-ray examinations (over a period of time, if necessary) are mandatory in the presence of a solitary metastatic lesion diagnosed on X-ray evidence alone. Aspirated pleural effusion should be carefully examined by cytologic or cell-block techniques. A solitary accessible skeletal lesion of doubtful nature should be biopsied by either needle or scalpel for the purpose of establishing diagnostic certainty.

X-ray examination of the spine, skull or pelvis (skeletal survey) is expensive and not routinely required unless the patient presents localizing signs or symptoms. There is little doubt that occasionally patients have been unfortunately subjected to radical mastectomy with latent metastatic deposits which were undoubtedly present at the time of operation. These most often occur in the chest, spine and pelvis, with liver metastases being a less likely locale. The rigors of radical mastectomy in these patients with silent metastases most probably shorten their period of postoperative survival.

Laboratory Studies

Blood Count. One of the most important preoperative deficiencies which may occur in cases of cancer is an inadequate amount of blood. At times this deficiency may be demonstrated by the hematocrit or hemoglobin level or by the red cell count. However, blood lack may not be clinically evident by these routine tests. It can be discovered only by blood volume determinations. This is particularly true if dehydration has caused hemoconcentration giving the appearance of normal blood values in the presence of a serious anemia. Numerous observers have emphasized the importance of blood volume determinations in preoperative patients who are clinically suspect.

Patients with an anemia are particularly poor candidates for radical surgery and require blood transfusion prior to operation. Riddell (52) determined the hemoglobin level prior to radical mastectomy and again on the fourth postoperative day in 55 patients who received no blood transfusion. The average fall in the hemoglobin level during this short postoperative period was 13.5 per cent.

Certainly the precautionary measure of blood grouping and cross-matching of all patients admitted to the hospital for possible radical breast surgery is a wise preoperative requirement. The facilities of an ever-ready blood bank are a credit to modern hospitals and a source of much comfort and security to even the most skillful of surgeons. Certainly the availability of blood or plasma may be of great benefit to the patient.

The work of Beling and his colleagues (6) among others has presented convincing evidence to show that failure to replace a depleted blood volume before during or after radical surgery may be a serious error of omission, particularly in elderly patients. The experience of most surgeons indicates that patients will tolerate radical mastectomy with a minimal amount of difficulty if adequate blood replacement is provided

Urinalysis Urinalysis is a routine preoperative procedure in almost all hospitals. If glycosuria is discovered, blood sugar studies are then performed to confirm the diagnosis of diabetes and establish its severity It is advisable that all diabetics be adequately controlled prior to undergoing major surgery

Blood Chemistry and Special Studies Blood chemistry examinations and electrocardiography are not normally performed preoperatively unless indicated However when radical mastectomy is contemplated on an elderly patient certain important additional laboratory information may be required The NPN and blood protein levels may be desirable and if fluid loss has occurred due to vomiting sodium, potassium and chloride determinations should be obtained Fluid and electrolytic balance should be corrected preoperatively whenever possible without undue delay An elevated alkaline phosphatase level may indicate liver damage or bone or liver metastases However many patients with extensive bone metastases have a normal alkaline phosphatase level

Conclusions

With proper preoperative precautions radical mastectomy may be safely performed in elderly women who are past the proverbial three score and ten However, some elderly patients with serious complications—hypertensive cardiovascular disease or diabetes with associated vascular damage—may more comfortably survive their limited life expectancy if their breast tumor is treated by conservative means. Whereas there can be no compromise with cancer yet in certain cases it is desirable to chart a course of treatment which avoids both Scylla and Charybdis

All surgeons recognize that under ordinary circumstances major operations on elderly patients are more dangerous than on sturdier patients in the prime of life However, as noted by Cole (12) if concurrent and complicating conditions can be eliminated the elderly woman with breast cancer will tolerate radical mastectomy quite well indeed for chronologic age is not always a true index of biologic stamina or physiologic reserve.

Blood Loss in Radical Mastectomy

It is a customary and advisable practice to begin intravenous fluids at the start of the operation if the biopsy report indicates the necessity for radical surgery The fluid is introduced at a moderate drip-rate and blood can be substituted for glucose in water or saline at any time The blood loss incident to radical mastectomy has been estimated in reports collected by Coller and his colleagues (13) to vary between 1,272 cc and 254 cc with an average of about 732 cc

The practical importance of blood loss during radical mastectomy has not been generally recognized Adequate provision for its replacement should be made The correlation which exists between actual blood loss and the recorded changes in the hematocrit, hemoglobin and plasma protein con

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centrations before and after surgery has been shown to be misleading and unreliable. There is no single test or clinical sign which will forecast impending surgical shock By the time shock is recognized, it is already well established However, the earlier the treatment, the better the results The most satisfactory method of therapy is to replace the blood loss as it occurs—planned transfusions during the operation

Coller and his colleagues have clearly demonstrated that blood loss determined by direct measurement is usually much greater than that estimated by the surgeon All studies indicate that it is essential to relate the amount of blood loss to the total blood volume Blood volume measurements by means of dye injection are not difficult to perform. For practical purposes, however, one-thirteenth of the body weight is blood, and a simple method of calculation is to allow 30 cc of blood per pound of body weight. In four cases of radical mastectomy, Coller found the average blood loss by direct measurement to be 821 cc or 17 7 per cent of the total blood volume The smallest amount of blood loss was 529 cc (14 6 per cent of the total blood volume) and the largest was 1,091 cc (25 8 per cent of the total blood volume)

In view of these direct measurement studies indicating a considerable blood loss during radical mastectomy (actual loss as well as in relation to total blood volume), it is recommended that most patients undergoing radical breast surgery receive between 500 cc and 1,000 cc of blood as a replacement during the course of the operation.

Preoperative Sedation

Having completed the basic diagnostic procedures, which consist of a complete history and physical examination including routine or required laboratory and X-ray studies, the patient is next prepared for operation by correcting any existing deficits and evaluating and reducing the risks of anesthesia Finally, on the evening before operation the preoperative orders for sedation are prescribed

The two general purposes of preanesthetic medication are (1) to present a well rested, serene patient to surgeon, (2) to minimize the dangers of anesthesia and surgery

A satisfactory night's rest is an important part of the preoperative preparation Most patients, anticipating major surgery or anxious about the possibility of cancer, are poor candidates for a good night's sleep A soporific of average dose given by mouth or by hypodermic may not be sufficient

The administration of preoperative sedation is important from several points of view. It relieves pain, if present, and reduces irritability It dulls the sensorium and reduces apprehension and anxiety Properly administered sedatives will lessen the likelihood of serious reactions due to prolonged operative procedures or to the anesthetic agent itself When certain anesthetic agents such as ether are anticipated, it is desirable to use premedicating drugs with a drying effect such as atropine or scopolamine Atropine also serves as a vagal depressant which tends to minimize the reflex stimulation of prolonged or major operative trauma

Barbiturates in place of narcotics are being used more and more as the preanesthetic medication of choice

Anesthesia

The patient undergoing radical mastectomy is of special interest from the anesthetist's point of view because of the lack of need for muscular relaxation, the possibility of considerable blood loss, and the state of mind accompanying this surgical operation

These patients are, almost invariably, quite apprehensive They are frequently

aware of the seriousness of their disease and, in addition are especially upset over the prospect of losing a breast As a result, both in kindness to the patient and to simplify the problem of anesthesia, they should be sedated somewhat more heavily than is usually the case In general the combination of a barbiturate the night before surgery and two hours before the start of anesthesia, with scopolamine and Demerol® one hour before anesthesia is desirable However, the choice of drugs and the dose will depend in each individual upon weight, physical age and general condition of the patient

The patient whose physical age is over 60 should receive a very small dose of morphine or Demerol® (3–4 mg. morphine or 25 mg Demerol®) or none at all The barbiturate can be used in all patients usually 100 mg of Nembutal® or Seconal® but, in the small, aged or debilitated patient, 50 mg will suffice

Scopolamine in a dose of 0 4 mg is desirable because of its sedative and amnesic effect. In the aged this drug sometimes produces a minor, transient psychosis and in this group atropine should be substituted in the same dose

The average sized healthy patient 40 to 60 years of age should receive

Nembutal®	100 mg night before operation
Seconal®	50–100 mg two hr preanesthesia
Scopolamine	0 4 mg one hr preanesthesia
Demerol®	25–50 mg one hr preanesthesia

After the administration of the scopolamine and Demerol® the patient should be watched closely since she may become unusually depressed and may need attention to the airway It is wise to remember that too little sedation before anesthesia is safer than too much and that this rule is of special importance in the aged If the patient is to receive cyclopropane anesthesia, the opiate should be omitted

On arrival in the operating suite the patient should be placed in a quiet darkened room under the observation of the anesthetist or a nurse

In our experience, most patients undergoing breast surgery do well with Sodium Pentothal® as the major anesthetic agent, supplemented by nitrous oxide in proportions determined by the adequacy of pulmonary ventilation Anesthesia should be induced slowly with small increments of Pentothal® (50 mg at a time), while the patient breathes oxygen

In most patients an endotracheal tube is passed after the induction of anesthesia This not only guarantees the easy maintenance of an airway but often permits the use of lighter planes of anesthesia Succinyl choline 30 mgm intravenously will provide sufficient relaxation for intubation When Pentothal® is the major agent respirations must be assisted throughout As the major part of the surgical dissection is completed the Pentothal® may be stopped and the patient carried on nitrous oxide and oxygen

An equally satisfactory technique is the use of very light ether anesthesia Little ether need be used and the necessity to assist repirations is eliminated If blood loss should get ahead of replacement, or if any other factor interferes with the maintenance of adequate cardiac output, satisfactory circulation is more easily maintained with light ether anesthesia than with Pentothal® For this reason many prefer light ether anesthesia *in all of these patients.*

It is our opinion that in the patient whose cardio-circulatory status is good at the start, if one maintains careful watch on blood replacement Pentothal® is perfectly safe The quiet induction and the relatively pleasant recovery period *characteristic of this*

drug make it the anesthetic of choice in the majority of these patients

For the asthmatic, ether should always be the major agent because of its bronchodilator action For the patient with a reduced blood volume, with poor cardiac reserve, or one who goes into shock during the procedure, cyclopropane should be the anesthetic agent

Regardless of the anesthetic drug or technique, only light planes of anesthesia are required, and deep anesthesia should never be used The patient should be awake as the dressing is applied, able to cough and move about on request

The question of blood loss and adequate replacement, an essential matter for the maintenance of safe anesthesia in these patients, is discussed in a separate section of this chapter (see page 255)

In recent years some clinics have favored the employment of drugs to induce deliberate hypotension during radical breast operations There can be no question but that this technique, when properly employed, will reduce blood loss and shorten operating time The occasional development of serious complications, associated with inadequate circulation to vital centers during the hypotension, has influenced us to reserve the technique of deliberate hypotension for operations which are extremely difficult or impossible to perform in the face of normal blood pressure We do not believe radical mastectomy belongs in this category

Skin Preparation

Among the many refinements of a sound surgical technique none is preferable to a deft and gentle touch This applies to the cleansing of the operative area as well as to the handling of the scalpel The vigorous massage of a breast malignancy while preparing the skin is a careless exercise

Satisfactory sterilization of the skin in the axilla, around the nipple and areolar regions and in the costo-mammary crease requires careful shaving and extra-special cleansing The use of ether followed by liberal and repeated applications of tinted Zephiran® chloride (benzalkonium chloride), either aqueous or tincture, gently applied with a sopping wet sponge stick, can be recommended as a satisfactory routine practice As yet the all-purpose, perfect skin antiseptic has not been discovered, but many other detergents, quaternary ammonium compounds, heavy metal antiseptics, soap and water or dilute solutions of iodine have been used with confidence and safety in the operating room (Lewison (31)) The skin of the anterior chest wall is extensively prepared, including the upper arm and a possible donor site on either the thigh or abdomen These areas are separately draped and covered.

As noted in the chapter on Breast Biopsy (Chapter IX), if the frozen-section report indicates malignancy, all contaminated instruments and soiled sterile drapes are discarded and members of the surgical team promptly change their gowns and gloves The special biopsy tray is removed, and the nurse who has remained free of contact with the biopsy procedure now takes her place at the operating table Complete or partial re-preparation of the operative area may be required in accord with the extent of cancer contamination during the biopsy procedure.

Most often the patient is draped for radical mastectomy at the onset of the operation This involves preparing an area which extends from the base of the neck to the upper abdomen and from the posterior axillary line to the opposite side of the sternum (fig 83) Preliminary biopsy does not usually require a subsequent complete re-draping However, when the clinical diagnosis is obviously a benign breast tumor, the patient

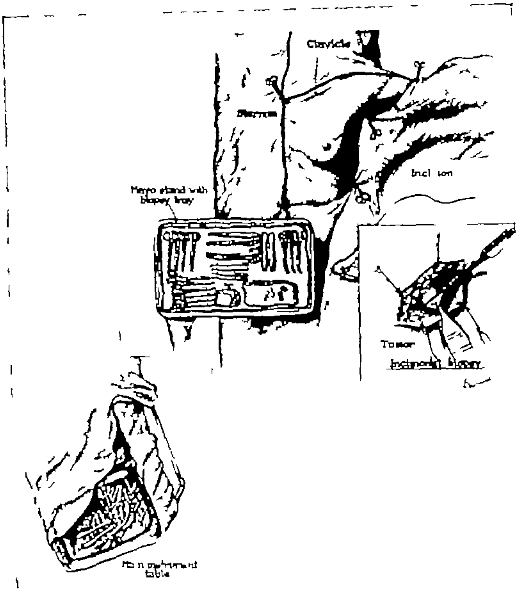

FIG 83 Sterile field draped for preliminary biopsy and frozen section Separate instruments used for biopsy on Mayo stand

may be draped less extensively than for a radical mastectomy

POSITION OF THE PATIENT

The patient usually lies flat on her back without the support of any pillows or sand bags beneath her shoulders I have seen several surgeons who have found it desirable to elevate the upper part of the operating table thus putting the patient in a semi reclining position The use of gravity aids in the operative exposure Sandbags or pillows beneath the shoulder occasionally aggravate postoperative pain in the back and shoulder due to poor position Both arms are outstretched on arm boards and fluids are administered or blood pressure readings are taken on the side opposite the site of operation

Tilting the operating table laterally upward on the side of the operation as suggested by Haagensen allows for greater posterior accessibility and facilitates the dissection of the lateral skin flap However in tilting the table laterally the position of the outstretched arm must be carefully pro-

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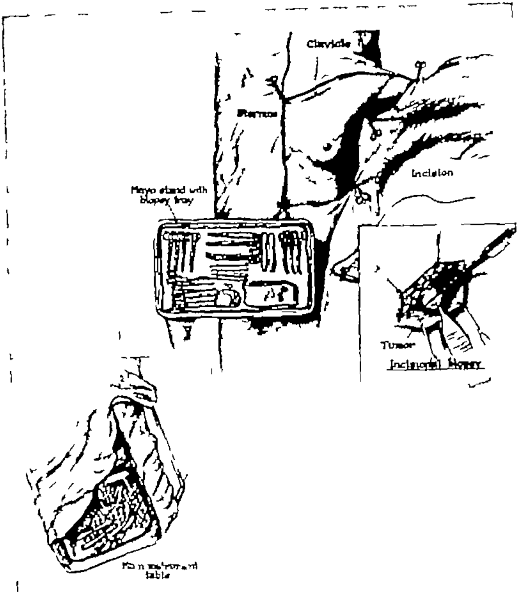

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tected to prevent undue stretching and possible neurovascular injury Returning the operating table to a level position at the end of the operation will decrease the tension on the skin flaps and facilitate their primary closure Adducting the arm will also aid in this maneuver

As emphasized by MacFee (38), radical mastectomy is an extensive operation which involves an undesirable amount of manual and instrumental handling It is quite possible to reduce some part of this manipulation by postural changes on the operating table However, substituting the force of gravity for adequate retraction appears to compound the complexities of this dissection

General Objectives of Radical Mastectomy

In discussing the surgeon's responsibility for the treatment of cancer, Dunphy (17) states that "the ideal cancer operation is one which widely extirpates the neoplasm with a generous margin of normal tissue, encompasses all adjacent zones of lymphatic spread and yet leaves the patient as nearly normal anatomically and functionally as possible At times function and anatomy must be sacrificed, but in return there should be reasonable expectation of a genuine and tolerably long improvement in the patient's condition"

The primary objectives in performing a radical mastectomy are the complete removal of the breast, its underlying pectoral muscles, and the axillary nodes, with the ultimate restoration of the patient to good health and normal function This operation is designed to accomplish this by means of a dissection in continuity and performed with a gentle and non-contusive technique Halsted (see Chapter I) advised and practiced the removal of the pectoral muscles leaving only the subclavicular portion of the pectoralis major He insisted that "all tissues should be removed in one piece and upon the meticulous cleaning of the axilla "

Since the operation of radical mastectomy was planned to eradicate breast cancer and its local spread to the axillary nodes, its technique must be radical and without compromise All skin within a perimeter of two or three inches (three or four finger-breadths) of the palpable edge of the breast tumor must be excised The breast in its entirety should be removed.

Many investigators have demonstrated the close proximity of the epithelium of the breast tissue to the overlying skin It has been shown that the subcutaneous plexus of lymphatics and breast epithelium (see Chapter II) lie within a mere matter of millimeters of the undersurface of the skin The superficial spread of breast tissue over the anterior chest wall is far wider and more significant than is commonly realized To leave this breast epithelium or plexus of lymphatics behind is to court the possibility of local recurrence Also, multicentric foci of breast cancer within this area may occur simultaneously in several separate parts of the breast Thus, the skin over the breast area must be dissected on a very superficial plane As little breast tissue as possible should remain adherent to the deep surface of the skin flaps

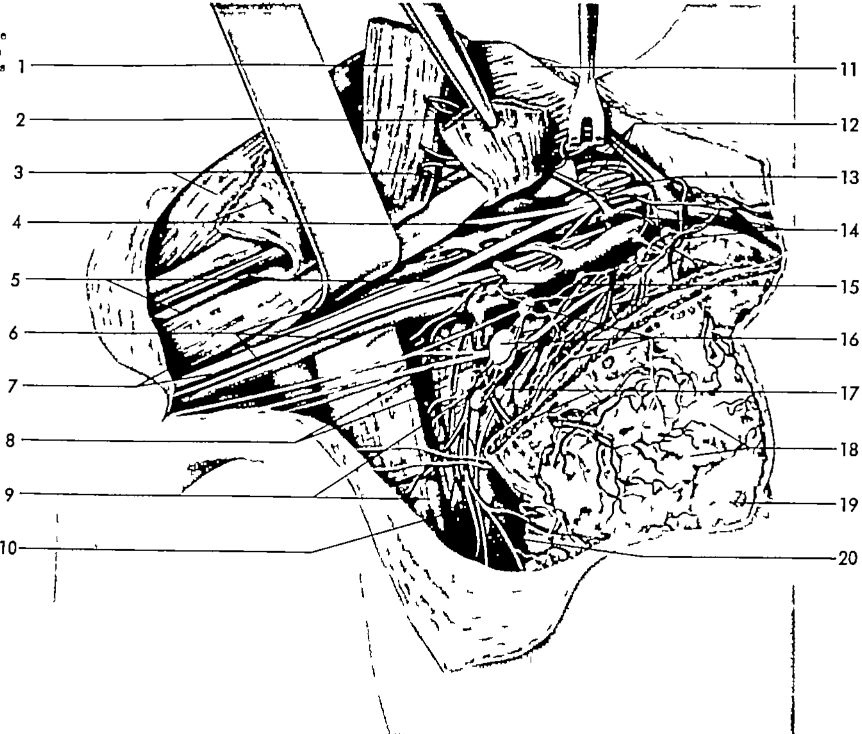
In the dissection of the axilla it is most important to remove all the fat, lymph nodes and areolar tissue which lie below the axillary vein In the routine radical mastectomy any dissection carried above the axillary vein to the axillary artery or brachial plexus is usually considered unnecessary and may result in a rare but very painful brachial neuralgia Extended radical breast surgery, however, may include a supraclavicular neck dissection in addition to a parasternal nodal excision

Hemostasis and the avoidance of local

Plate IV

Illustration of the anatomy of the breast and exposed axillary region (Courtesy of Lederle Laboratories Division American Cyanamid Company)

1 Pectoralis major muscle
2 Pectoralis minor muscle
3 Deltoid muscle cephalic vein
4 Pectoralis major muscle musculocutaneous nerve
5 Long head of biceps brachii muscle lateral branch of median nerve
6 Brachial artery and vein ulnar nerve
7 Short head of biceps brachii muscle median nerve
8 Intercostobrachial nerve subscapularis muscle
9 Thoracodorsal nerve latissimus dorsi muscle
10 Branch of thoracodorsal artery
11 Acromial extremity of clavicle
12 Suprascapular artery vein and nerve
13 Thoracoacromial artery
14 Axillary artery and vein subclavian lymphatic trunk
15 Medial branch of median nerve lateral thoracic artery
16 Axillary lymph nodes pectoralis minor muscle
17 Long thoracic nerve pectoralis major muscle
18 Lobes of breast
19 Papilla of breast
20 Thoracoepigastric vein



infection are both of considerable importance in wound healing and of paramount concern in preventing postoperative lymphedema of the arm. The silk technique first favored by Halsted is recommended as a measure of gentleness and to assure minimal tissue reaction. Fine silk sutures of 2-0 and 4-0 are most frequently used for ligatures and sutures.

Operative Technique for Radical Mastectomy

Incision

The skin incision for radical mastectomy is planned so that the tumor is the center of an elliptical or circular island of skin which should always include the nipple. The preliminary outline is etched on the skin with a cotton swab, needle or the back side of a scalpel blade and its position depends to some extent upon the configuration of the breast, the position of the tumor and the location of the previous biopsy incision. The outlines of this perimeter should be well beyond the biopsy incision which is usually radial and must never be encroached upon. The remainder of the incision is a linear vertical extension running upward in the strap line to just above the coracoid process and downward in the direction of the umbilicus but ending just below the costal margin.

Biopsy incisions in the breast parenchyma should be radial to the nipple in order to avoid serious injury to the main ducts should the lesion prove to be benign. The skin incision need not be in the same axis as the incision into the breast tissue but it should be planned to be cosmetically inconspicuous and to interfere *as little as possible* with subsequent radical mastectomy. A radial incision in the breast tissue with an overlying skin incision at right angles to it may require an undesirable degree of forceful retraction for adequate exposure. Marginal biopsy incisions have been used by some surgeons because they *follow the normal tension lines* of the skin (Langer's lines). However, these marginal incisions may subsequently contaminate or interfere with the planning of the more important radical mastectomy incision. Tumors which are adjacent to the areola may be readily exposed for biopsy by a Y shaped or crescent incision at the edge of the areola. Submammary incisions in the costo-mammary fold are inconspicuous, preserve the nipple and are useful for tumors located at the lower margin of the breast.

Many types of incision for radical mastectomy (figs. 85 and 86) have been used and all have proved useful under certain circumstances and advantageous in the hands of their particular sponsors. The numerous variations that have been described, however, indicate that no single incision alone has been found ideal for all cases of breast cancer. Orr (47) has suggested five criteria which might serve as a guide in selecting a satisfactory incision. These are as follows (modified after Orr):

1. The incision must remove sufficient skin to be reasonably sure of excising all ramifications of the tumor.
2. It must provide adequate exposure for removal of the entire breast and the tumor.
3. It must provide excellent exposure for the complete axillary dissection.
4. It should allow skin closure with as little tension as possible.
5. The incisional scar should never encroach upon the axilla or extend onto the arm where contracture and disability may result.

A simple transverse incision described by *Stewart (59) (fig. 86) has been found by some* surgeons to be quite useful. Although the axillary exposure is perhaps more difficult and somewhat restricted, closure is facilitated, healing is good and mechanical interference with the axilla is avoided. This incision is particularly useful in tumors located

Fig 84 A, B, C and D Original and previously unpublished (A, B and C) drawings of Halsted's many modifications of his initial incision These drawings were in the early transitional period and were by the distinguished medical artist, Mr Max Brödel At a later date Halsted abandoned the triangular upper flap, as well as the incision onto the shoulder, finally using a simple oval incision with a short upper and lower vertical extension

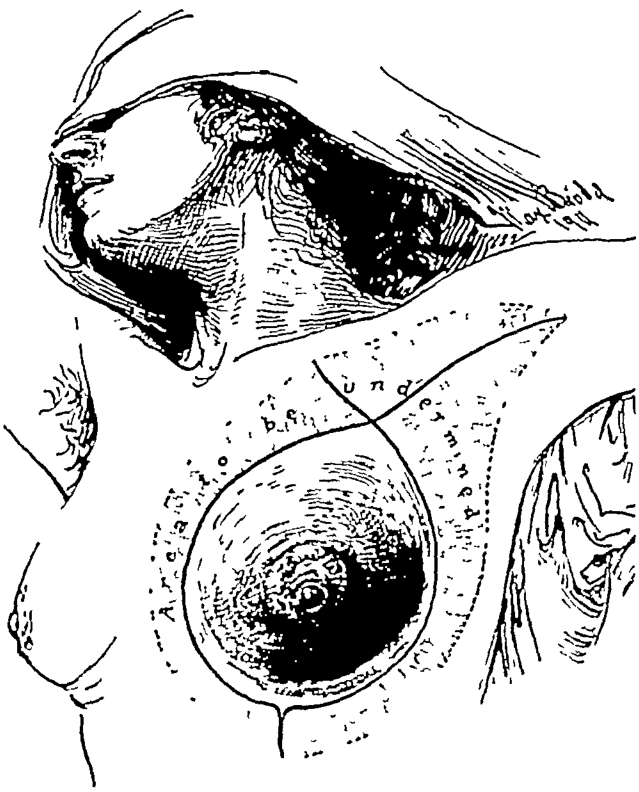


Fig 84 A

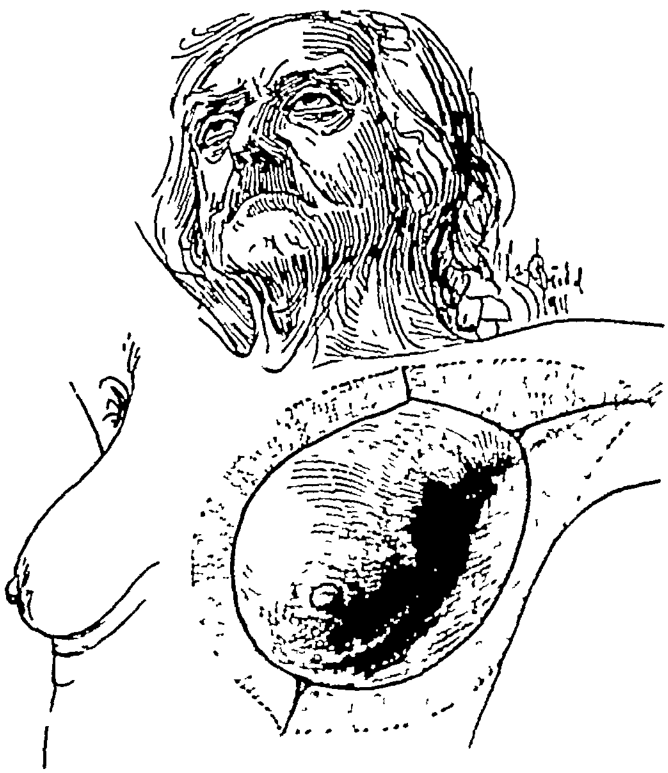


Fig. 84 B

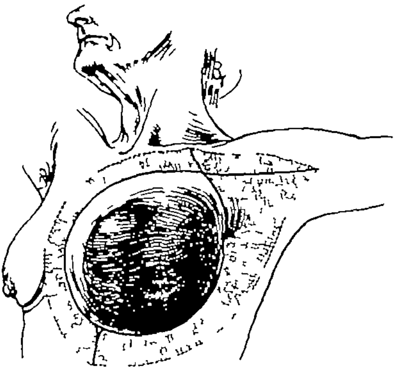


Fig 84 C

Fig 84 D

in the extreme lateral or medial margins of the breast

The Rodman or Greenough arrowhead incisions (figs 85 and 86) are quite similar and are of special value in tumors which are located high in the axillary tail Here the care and protection of the exposed axillary vessels is of special concern Lymphedema is said by Daland (15) to be less with this type of an incision which is well below the shoulder and upper axilla.

An oblique subaxillary S-shaped incision

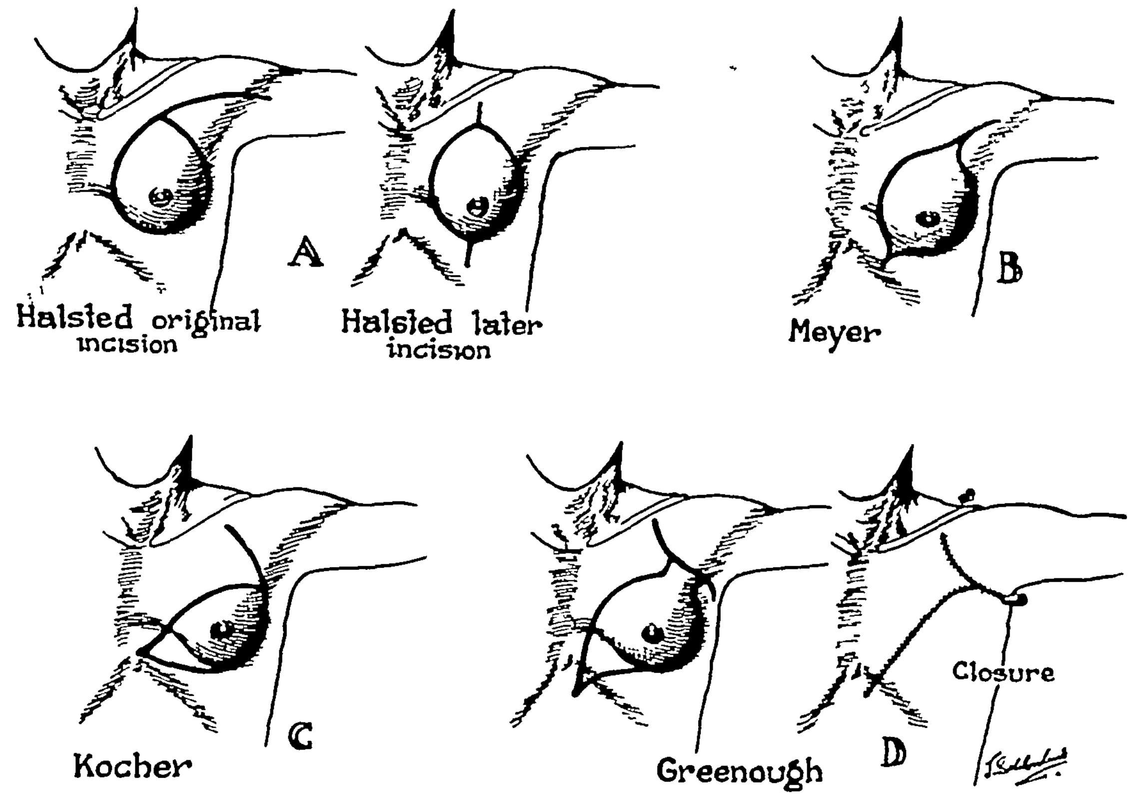


Fig. 85

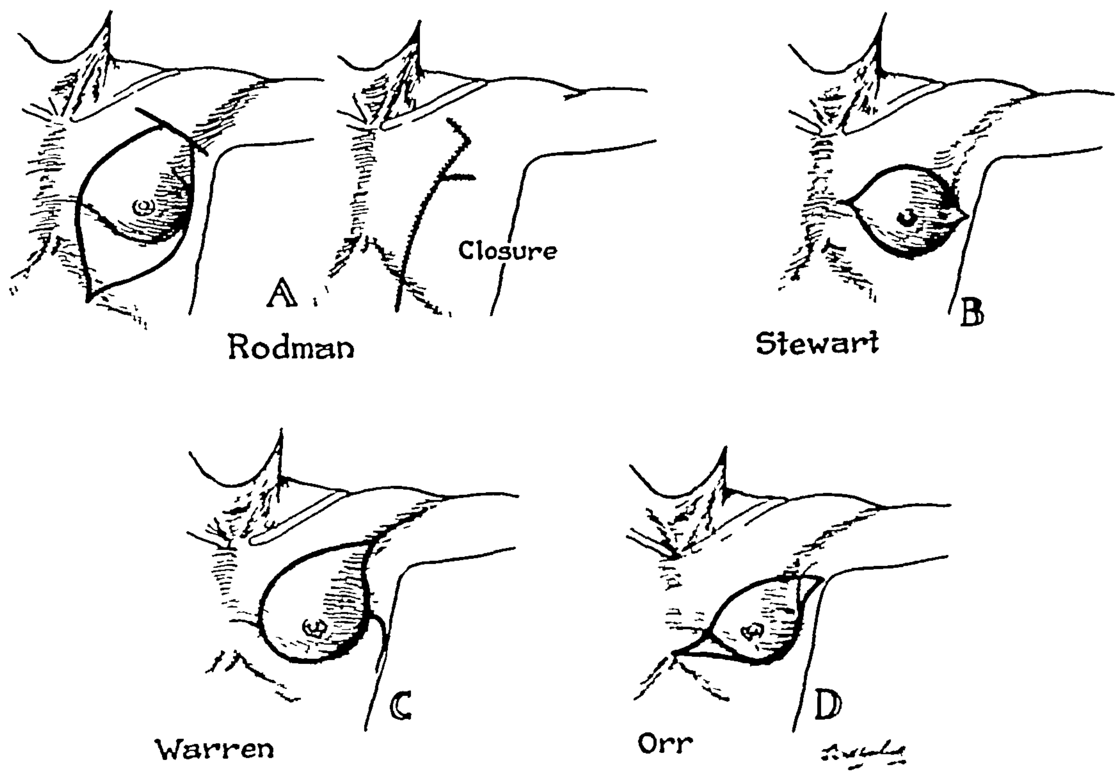


Fig 86

Figs 85 and 86 Many types of skin incision for radical mastectomy have been advocated, and all have proved useful under certain circumstances and advantageous in the hands of their particular sponsors Modifications are made to permit better exposure, facilitate closure or for cosmetic reasons The numerous variations indicate that no one incision is ideal for all cases The Orr incision (86D) had been described earlier by Leighton and subsequently by MacFee The standard incision used by most surgeons is the Halsted later incision or the Meyer incision

(fig 86) has been described first by Leighton (29) and later by Orr (47) and MacFee (39) This incision permits a slightly better axillary exposure than a simple transverse incision and places the resultant scar in a location where it does not interfere with arm function or constrict the axilla As described by MacFee this incison affords good exposure and occupies a concealed position

The incision which is most commonly used resembles Halsted's later incision (fig 85) and consists of two linear portions above and below the breast joined by an ample elliptical portion encircling the breast The dermal and subcutaneous plexus of lymphatics overlying the tumor make it mandatory to remove a wide area of skin. The upper and lower linear extensions of this incision lie in a straight line (Halsted was among the first to abandon the curved incision over the shoulder) from just below the clavicle at about the level of the coracoid process in the strap line downward and a little toward the midline until it reaches the upper border of the anterior rectus sheath at the costal margin The exact points where these lines divide and rejoin to surround the breast are determined by the location of the tumor and the size and shape of the breast *A margin of at least two inches (three or four fingerbreadths) from the palpable edge of the tumor on all sides must be maintained* Actual measurement of this distance is recommended There is good evidence to indicate that if a wide skin excision is to be successful for small tumors a much wider excision must be made for larger tumors.

The incision which curves up over the shoulder has been found by experience to be unsatisfactory With the removal of the pectoral muscles and the distortion of the upper end of the incision incident to tension and movement of the arm subsequent to surgery there often occurs a migration of the scar into the axilla. In this position it lies over or crosses the neurovascular trunk and may produce severe pain and disability by subsequent scar contracture Riddell (53) warns against functional disability which results from skin displacement It is not desirable to borrow skin from the axilla and upper arm to close the axillary part of the incision

The previous biopsy incision should be carefully placed with ultimate radical mastectomy in mind McGraw (30) cautions against the mistake of making the biopsy incision a part of a larger incision for radical mastectomy This must *never* be done Any contamination from the biopsy wound is to be scrupulously avoided by means of rigorous "cancer asepsis"

Skin Removal in Radical Mastectomy

Halsted (21) was among the first to advocate a wide removal of skin, making it necessary to graft the denuded anterior chest wall in almost all patients undergoing radical mastectomy In 1912 he discussed the developments of the skin grafting operation and said "For about sixteen years our practice has been to cover the fresh defect made as small as feasible in various ways with large Thiersch grafts. The available skin was tucked high into the armpit in order to cover the axillary vessels, to obliterate the dead space under the clavicle and to elevate to the highest possible point the axillary fornix."

Halsted described in detail the reasons for recommending skin-grafts in radical breast surgery From these early observations made at the Johns Hopkins Hospital it seemed that the results were better in cases where large areas of skin were removed According to the statistics of Bloodgood (referred to by Halsted) it would appear that of the various surgeons performing radical mastectomy the best results were obtained by those who made a practice of giving the tumor the widest berth in making the

skin incision. However, these same surgeons may have also performed a more thorough operation in other respects. Halsted believed that it was better to remove too much skin than to remove too little. For the error of insufficient skin excision was a gross fault and seriously lessened the patient's opportunity for permanent recovery. "Nothing is gained, therefore, by saving skin which, either because it is too close to the cancer or by reason of impairment of its circulation is questionable."

Handley, an English contemporary of Halsted's, favored a very limited amount of skin removal in the belief that breast cancer spreads by permeation and contiguity through the vertical and fascial lymphatics.

Today the problem of skin removal still remains the subject of much controversy. It is, of course, a most important matter because ostensibly it appears to have a direct bearing upon local recurrences, ultimate end-results and the immediate technical problem of primary skin closure versus primary skin-grafting. However, in our present state of imperfect knowledge it can only be said that local recurrences are observed with distressing frequency and that there is no clear-cut evidence to suggest that any one factor in operative technique is of major importance compared to another in preventing these evil lurkings.

Lewis and Rienhoff (30), in a review of the early Johns Hopkins Hospital cases, concluded that surgeons must perform a wide skin resection, even wider than had been customary with the original Halsted technique. These authors believed that by this method alone surgeons could decrease the incidence of local recurrences to its irreducible minimum.

The fact that local recurrences are found commonly in the skin of the chest wall immediately adjacent to a grafted area suggests that even in grafted cases insufficient skin had been sacrificed at the primary operation. Among the many reasons for failure to remove a very wide margin of skin, one of the most important is the surgeon's reluctance to leave the patient with a large defect requiring a time-consuming and laborious skin-grafting closure. Halsted, in 1907, quoted the now classic remark of his house-officer, Dr. Richard Follis, that "the operator whose duty it is to close the wound should not be intrusted with the planning of the skin incision." While subcutaneous tissue, breast parenchyma and musculature may be excised freely from the thoracic wall, the necessity for incisional closure restrains the surgeon from performing a wide excision of skin.

Conway and Neumann (14) have reviewed a series of 255 patients subjected to radical mastectomy at the New York Hospital. The local recurrence rate was compared (1) in those patients in whom a skin-graft was used in closure, and (2) in those patients in whom a skin-graft was not used in closure (primary closure). Local recurrences developed in 44 patients or 17 per cent of the entire series. In 188 patients in whom a graft was employed in closure, there were 40 instances of local recurrence, or a recurrence rate of 21 per cent. In 67 patients in whom a graft was not employed in closure, there were only four instances of local recurrence, or a recurrence rate of six per cent.

To be certain that this difference was not due to the possibility that skin-grafting had been used more frequently in large tumors (where local recurrences have been shown to be more frequent), the tumors were divided into two groups according to size. In 151 cases of small cancers (less than seven cm.) which *were* grafted there was a local recurrence rate of 16 per cent. In 62 cases of small cancers (less than seven cm.) which *were not* grafted there was a local recurrence rate of only six per cent.

In the development of local recurrence following radical mastectomy, the presence of axillary metastases at the time of operation is known to be a factor of considerable importance Of the 107 patients with axillary metastases who received skin grafts, 27 patients developed local recurrence a rate of 25 per cent Of the 81 patients without axillary metastases who received skin-grafts, 13 patients developed local recurrence a rate of 16 per cent. However of 32 patients with axillary metastases who were closed *without a skin-graft* local recurrence occurred in only two patients, a recurrence rate of six per cent

In 40 instances of local recurrence following skin-grafting 67.5 per cent appeared as solitary nodules surrounding the grafted area. Because of this proximity of local recurrences to the graft Conway and Neumann concluded that a more radical excision of skin might give further protection against local recurrence' This particular partisanship is not entirely confirmed by their own data.

In a study of 254 cases of breast cancer White (64), an excellent surgeon long interested in the problem of local recurrence found a recurrence rate of 22 6 per cent in 238 cases of primary or plastic closure Among 17 cases of skin-graft closure the local recurrence rate was 35 per cent The results of radical mastectomy in relation to the type of closure and local recurrences have been compared by White (65) (table 41)

Although one must evaluate the variations in these data in a very broad way yet it is apparent that regardless of the actual extent of a wide' skin removal or the type of subsequent skin closure there remains a relatively high incidence of local recurrences.

At the Mayo Clinic Harrington (24) believes that most skin incisions can be closed primarily with little or no danger of recurrence in the skin Marshall and Hare (40) have intentionally limited the extent of skin removal in order to obtain early primary healing for the purpose of administering early postoperative radiotherapy By this procedure they enhanced their five year survival rate and noted local recurrences in only eight per cent of their patients

Cogswell (11) has carefully reviewed the literature and came to the logical conclusions that, one can usually plan a primary closure of the wound after a radical mastectomy without decreasing the survival years and in fact with the hope of increasing them by allowing postoperative irradiation to begin at an earlier date It is of course impossible

TABLE 41

	No.	Local Recurrence No.	Local Recurrence Per cent	5 yr Survival No.	5 yr Survival Per cent
Roosevelt Hospital (New York) (White (64))					
Primary closure					
Breast alone	101	11	10 8	62	61 0
Axillary metastases	137	43	31 5	25	17 0
Presbyterian Hospital (New York) (Haagensen and Stout (19))					
Primary closure and skin graft					
Breast alone	237	23	9 7	145	61 2
Axillary metastases	385	120	31 3	81	21 0
Johns Hopkins Hospital (Lewis and Rienhoff (30))					
Primary closure	116	46	39 7		
Skin-graft	322	97	30 1		
Henry Ford Hospital (Hoopes and McGraw (27))					
Primary closure					
Breast alone	73	4	5 5		
Axillary metastases	82	13	16 0		
Skin-Graft					
Breast alone	24	2	8 3		
Axillary metastases	67	18	27 0		

Modified after White (1946)

to perform a primary closure in every patient A number of technical factors are known to mitigate against primary closure The amount of skin to be removed is a problem of sound surgical judgment Closure so often depends upon the site and size of the tumor, the size of the breast and the local or systemic conditions of the skin and circulation.

However, if the incision is carefully planned according to the location of the tumor, with the distance between the palpable edge of the tumor and the incision no less than two inches (five cm), most wounds can be closed primarily without undue tension

Although some local recurrence following radical mastectomy may be due to gross errors in surgical technique, or possibly exceptionally cordial host hospitality, White believes that despite the utmost surgical solicitude it is almost impossible to remove all cancerous tissue The fact that the local recurrence rate of breast cancer even after satisfactory radical mastectomy is all too common, regardless of surgical skill, bears out the belief that certain cases have undetectable microscopic extension of the disease which is often left behind Selective vital staining of cancer cells prior to surgery may some day help to prevent this serious ineptitude. The use of dyes, fluorescent and radioactive compounds are being used in clinical investigative studies

In the performance of tumor surgery, it is important to avoid the transplantation of cancer cells by meticulous "cancer asepsis" Ryall (54) in 1907 and Ewing, Saphir and Brandes (8, 18, 55) more recently have warned against the accidental transplantation of cancer to a fresh donor site during radical mastectomy Saphir and Brandes both have studied the washings from contaminated instruments and gloves during radical mastectomy and demonstrated the presence of viable cancer cells with unexpected frequency.

Summary. A review of the literature indicates that there is no conclusive evidence that a skin-graft closure will assure greater freedom from local recurrence than a primary closure With proper technique a wide margin of skin (two inches from the edge of the tumor on all sides) can be removed in most cases and yet provide the opportunity for primary closure Where the skin edges cannot be approximated safely without undue tension, immediate skin-grafting is certainly the closure of choice

Elevation of the Skin Flaps

The anatomy of the breast lymphatics (see Chapter II) favors the elevation of the skin flaps by cutting them as thin as possible However, the wide undermining of skin at the superficial level of the dermal lymphatic plexus which lies within the corium is technically difficult and practically unfeasible Damage to the blood supply of these tissue-thin flaps is almost inevitable, and closure with only moderate tension often results in an extensive skin slough. Thus, this superfine dermal dissection frequently requires a large area of primary or secondary skin-grafting

In performing a fastidious dissection of the lateral skin flap in particular, one is likely to compromise its blood supply because of the vascular interruption incident to a complete axillary dissection The medial flap is more generously supplied by perforating branches of the internal mammary artery and rarely is the site of skin necrosis

Yet it is an absolute desideratum of this dissection to elevate the flaps with as little fat and breast tissue attached to the undersurface of the skin as possible Thus, the level of dissection is carried out in a plane superficial to the subcutaneous tissue and subcutaneous blood vessels, but at about the

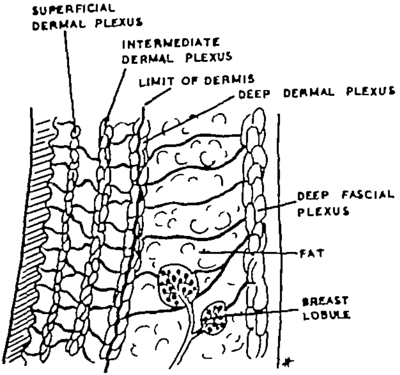


FIG 87 Diagrammatic relationship between the lymphatic plexuses of the breast and the skin (After Handley)

level of the deep dermal lymphatic plexus (fig 87) A little experience is often required to carry the initial incision through the skin and into but not through the subcutaneous tissue This exacting part of the operation is time-consuming and tedious but should never be neglected or undertaken carelessly *Working perhaps with slightly thicker skin flaps*, Adair (1) has described the technique of his dissection as appearing 'like a mouse under a blanket.'

Halsted emphasized the importance of thin flaps especially in the axilla—'there is nothing but skin in this flap Willy Meyer (43) advocated the "reflection backward of the three skin flaps with as thin a layer of underlying fat as possible leaving just enough so as not to endanger a future necrosis of the flaps." Other surgeons have recommended thin flaps at the incision edge with the dissection carried somewhat deeper by beveling the plane of dissection to the base of the flaps

To facilitate this dissection, Atkins (4) has suggested that the plane between the skin and subcutaneous tissue be infiltrated with a solution of 1–500 000 adrenaline in normal saline This wide infiltration serves a twofold purpose 1) it defines rather precisely the plane of skin reflection so that the dissection can be done with greater certainty at the correct level and 2) it renders the elevation of the flaps nearly bloodless. The *dangers of cancer cell dissemination by this* injection technique is considered highly unlikely by Atkins.

Among some surgeons there appears to be a growing tendency to decrease their operating time and modify their radical mastectomy technique by using thicker and shorter skin flaps. All surgeons experienced in the thin flap technique have been at one time or another distressed by the problems of delayed wound healing fluid accumulation beneath the flaps and marginal skin necrosis Any surgical expedient designed to prevent these disturbing complications would be most welcome providing of course that there is no compromise with cancer Although the advocates of the short thick-flap technique claim that they remove as much skin as by the conventional method (but

probably considerably less breast tissue), the short thick-flaps closed under rigid tension usually result in primary healing with fewer postoperative complications or prolonged convalescence However, convenience of closure must not take precedence over possible "cure" of cancer

Although some surgeons favor the complete axillary dissection prior to defining the skin flaps (thus severing early in the operation possible pathways of cancer dissemination), this has not been our policy Dissection of the axilla at the start of the operation is also considered advisable in order to avoid unnecessary or prolonged exposure of the denuded chest wall if this part of the operation is done after dissection of the chest wall The shocking part of the operation is thus delayed Also, the control of bleeding has been considered easier if the axilla is dissected early. The en bloc dissection or complete surgical excision in continuity can be successfully performed by either technique However, in our experience, complete surgical exposure prior to axillary dissection allows for a more meticulous cleansing of its contents

Dissection of the Lateral Flap

The dissection of the lateral skin flap is usually made first beginning at the distal or inferior end The scalpel penetrates the skin but only the superficial layer of subcutaneous tissue The lateral skin edges are lightly grasped with Allis clamps although small hooks can be used With taut traction being applied to the Allis clamps on the lateral skin margin, the subcutaneous undercutting of the flap is carried lateralward away from the incision in a very superficial plane (devoid of all but the thinnest layer of fat) Countertraction applied to the breast by means of clamps or small blunt "rake" retractors must be gentle and noncontusive The countertraction should be made without undue pressure on the breast or the chest wall and never across the breast itself The risk of disseminating tumor emboli is thereby diminished The use of heavy tenacula for traction is to be deplored Hand retraction by an assistant has a tendency to produce undesirable pressure on the tumor

During this early stage of the operative procedure great care should be exercised in regard to hemostasis The control of bleeding from major vessels severed in subsequent stages of radical mastectomy is considerably easier than the control of diffuse bleeding from many small vessels encountered during the extensive elevation of the skin flaps Persistent oozing, if neglected, can result in a moderate amount of unnecessary blood loss even if the plane of the dissection is quite superficial

All bleeding points on the undersurface of the lateral flap are ligated with fine black silk (4-0) which is used as ligature material throughout most of the operation Electrocoagulation is only used on the side of the breast which is to be removed

The control of bleeding during elevation of the lateral flap has been accomplished also by direct gauze sponge pressure or indirect finger pressure along the margin of the incision Riddell (52 and 53) recommends this technique and suggests that with "practice and the determination not to use artery forceps, the method will be found easy to apply, and will reduce blood-loss to an absolute minimum " However, it has been our practice to discourage pressure applied to the field of operation and in its place we prefer to use Halsted hemostats for the control of bleeding from the undersurface of the lateral flap

In the raising of the lateral flap back to a point opposite the outer border of the latissimus dorsi muscle, the problem of maintaining an even thinness throughout is difficult and usually requires time and a

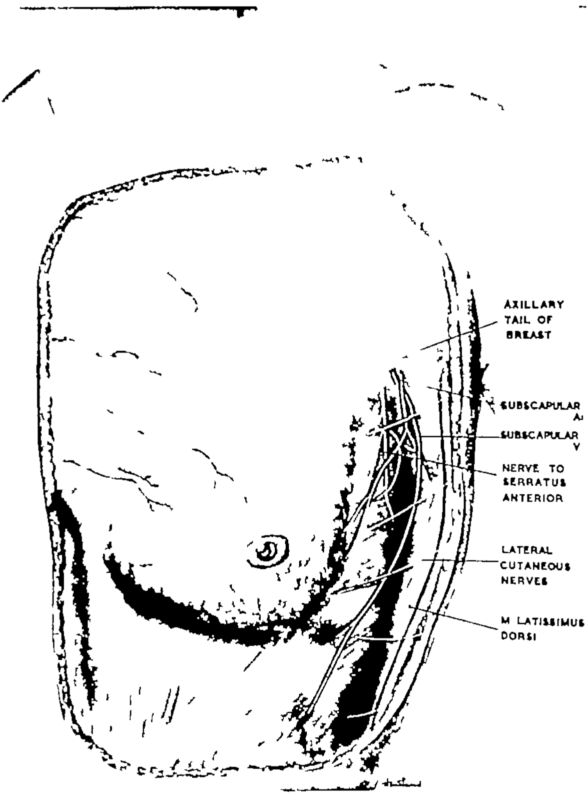


Fig 88 Preliminary dissection of the breast and lateral chest wall (After Handley)

considerable degree of patience If large lobules of fat and breast tissue are left adherent to the undersurface of the skin the resulting flap will be too thick This is particularly prone to occur if the dissection is performed with speed as a major objective

The error of elevating a thick flap may cause the surgeon further trouble by his continuing the deep dissection beneath the lateral border of the latissimus dorsi muscle rather than above it Failing to find this landmark (muscle edge), the surgeon may then encounter serious bleeding from the subscapular vessels which are large and somewhat inaccessible at this stage

In obese patients it is particularly important to dissect a thin axillary flap Contaminated axillary lymph nodes may be easily left behind unless this flap is thin enough to expose the dark hair follicles and amber colored axillary apocrine glands in this region An extensive axillary flap dissection is required for adequate exposure particularly if the incision does not curve over the shoulder

However if the dissection of the lateral flap proceeds on too superficial a plane there is serious danger of laying bare the white undersurface of the skin or even button holing' it Should this occur over a wide enough area the blood supply will be impaired and a greater or lesser skin slough will result A small margin of superficial skin necrosis often occurs at the incisional border of the lateral flap This is especially true if the dissection is extensive and the wound closed under tension

Although these factors of technique may seem trivial yet if even a small cluster of tumor cells is left behind needlessly or if convalescence is unduly prolonged because of extensive necrosis the complication may assume a more or less serious consequence

The lateral flap is dissected back to the landmark of the outer edge of the latissimus dorsi muscle Here the dissection is turned inward to expose the muscle edge In an obese patient this may require the incision of several centimeters of fatty areolar tissue Following this muscle edge as a guide upward (cephalad) it will lead directly to the crossing of the overlying edge of the pectoralis major muscle at a point proximal to its attachment to the humerus At this point care must be taken to avoid the axillary vein which is usually quite well protected beneath the pectoralis major muscle but may be exposed during inadvertent deep dissection The exposure of the fascia at the base of the axillary pyramid at this point may be anatomically confusing The presence of several large blood vessels adds to the difficulties of the dissection Continuing upward the dissection crosses the anterior surface of the pectoralis major which extends out on the arm This is clearly defined and the cleft between it and the deltoid muscle is recognized by the cephalic vein At the opposite lower end of the incision the anterior rectus sheath is now exposed

Dissection of the Medial Flap

In the classic radical mastectomy the next step is the elevation of the medial flap The same surgical principles are observed here as were followed for the lateral flap An equally delicate layer of subcutaneous fat is left attached to the undersurface of the thin medial skin flap Retraction of the breast proper can be dispensed with for the most part since gravity will usually cause the breast to fall away laterally from the field of operation. The dissection extends from the anterior rectus sheath below medially to the mid-sternum or beyond and upward to the clavicle In medial hemisphere tumors the dissection is frequently carried somewhat further toward the contralateral side The undercutting stops at the lower border of the clavicle, care being taken to avoid the

large cervical veins which lie above this level Hemostasis is carefully secured by fine silk ligatures (electrocoagulation is used on the breast side) and both skin flaps (lateral and medial) are then wrapped above and below in large warm saline packs

A modification of this technique useful for elevating the medial flap has been recommended by both Riddell and Atkins It consists essentially of leaving the reflection of the medial skin flap (except for its clavicular portion) to the last stage of the operative procedure In obese patients where exposure is difficult this modification is *not* advocated There are certain definite advantages to be gained by delaying the elevation of the medial flap as opposed to performing this step early in the operation Reflection of the medial flap early means dividing the same perforating branches of the internal mammary artery several times before they terminate in the skin By delaying the reflection of the medial flap (except at its upper portion), bleeding is reduced and the flap can be raised later in the operation with minimal bleeding This is so because these vessels already have been ligated when they pierced the pectoral muscles from below Thus, time is conserved and blood and heat loss are reduced

The object of raising the upper end of the medial flap is to facilitate the exposure of the sternal origin of the pectoralis major muscle By allowing its division opposite the first two interspaces, ready access is provided to the apex of the axilla

A similar expedient can be made use of by resorting to an initial partial dissection of the medial flap just short of the sternum where the cutaneous branches of the internal mammary artery emerge These branches can be secured later when the pectoralis major is completely removed.

In women with large, obese or pendulous breasts this procedure restricts adequate exposure and hinders the axillary dissection

Dissection of the Chest Wall

Division of the Pectoralis Major Muscle. The elevation of the skin flaps having been completed, the next step in the operative procedure is the division of the tendinous attachment of the pectoralis major muscle This is done just proximal to its insertion on the lip of the intertubercular sulcus of the humerus The removal of the pectoralis major allows a partial uncovering of the anterior wall of the axilla in order to gain access to its inner contents

Technique among surgeons may vary but in many of our cases only the sternocostal or sternal head of the pectoralis major is removed, leaving the clavicular portion intact However, if the tumor lies high in the upper hemisphere of the breast, it is advisable to remove both the sternal and clavicular portions of the pectoralis major muscle Regardless of which technique is followed, *all* of the pectoral fascia and overlying platysma containing the deep fascial lymphatic plexus (see Chapter II) which lies on the anterior surface of the muscle must be excised

The desirability of leaving the clavicular head of the pectoralis major depends upon the anatomicopathologic convictions of the surgeon (see Chapter II) Allowing the clavicular portion of the muscle to remain reduces the risk of lymphedema, adds to the postoperative cosmetic appearance of the infraclavicular "hollow" and provides for a functionally more useful arm However, these considerations would be a poor substitute for prudent surgery if it were shown that prognosis was adversely affected by this procedure Yet, there is no indication in our present state of imperfect knowledge that tumor recurrence or metastasis is in any way influenced by this detail of technique Despite the preservation of the clavicular

portion exposure of the apex of the axilla is usually adequate if gentle traction on the muscle is made with a smooth retractor

The chest wall dissection is begun by exposing the surface of the pectoralis major in the lateral infraclavicular fossa. This exposure of the muscle is carried downward below the clavicle a very short distance until the dividing line between the clavicular and sternal portions of the muscle is reached In some instances this line of demarcation is not easily found and in other instances there may be two rather distinct muscles. Where there seems to be a single muscle without a line of separation Bartlett (5) recommends finding the dividing line by exposing the surface of the pectoralis major muscle until one locates perforating vessels which usually lie in the line of cleavage These are branches of the thoraco-acromial leash of vessels. Separation of the muscle fibers can be made at this point

When the line of cleavage is found a finger is inserted between the muscle fibers and the artificial gap is widened (care being taken to avoid deep bleeding) Finger dissection is carried down to the insertion of the muscle on the humerus With the aid of adequate outward retraction of the lateral flap a finger is passed from the line of cleavage down under the main muscular mass of fibers until it emerges through the axillary fascia at the lower border of the muscle The tendinous attachment of the sterno-costal portion twists and inserts posterior to the clavicular portion of the muscle The muscle is then cut across usually between Kocher clamps close to its humeral insertion Elevation and separation of the muscle before clamping prevents possible injury to the underlying axillary vein or brachial plexus.

The leaving of a long stump of muscle attached to the humerus always means a visible and unsightly bulge which the patient may suspect of being residual or recurrent tumor Bleeding from this muscle mass will cause local ecchymosis, swelling pain and possible infection The thickness of the mass of muscle fibers at their point of division will vary among individuals depending upon occupation muscular development and right or left handedness The stump is carefully ligated to secure the several small bleeders which are almost always present Individual ligatures may be preferred if the muscle division is not made between clamps

If the entire pectoralis major muscle (both the sterno-costal and clavicular heads) is to be removed, then the cephalic vein which separates the deltoid muscle from the pectoralis major muscle is identified and followed laterally as the anatomical guide or landmark The tendon of the pectoralis is separated from the deltoid near its insertion into the lip of the intertubercular sulcus or bicipital groove of the humerus and severed as described previously without injury to the cephalic vein or its branches

Dissection of the Pectoralis Major Muscle from the Chest Wall As the severed attachment of the body of the pectoralis muscle is drawn medially, the anterior covering of the axilla becomes partially removed This exposes the clavipectoral fascia and costo-coracoid membrane (known also as the deep pectoral fascia) and the underlying pectoralis minor muscle (fig 89)

The medial anterior thoracic (pectoral) nerve which supplies the pectoralis minor muscle pierces it and helps to innervate the pectoralis major The lateral anterior thoracic (pectoral) nerve so-called because of its origin from the lateral cord of the brachial plexus and not from its lateral position perforates the clavipectoral fascia at the medial border of the pectoralis minor and is distributed to the undersurface of the pectoralis major (fig 90) This nerve runs in close proximity to the pectoral branch of the thoraco-acromial artery If the clavicular

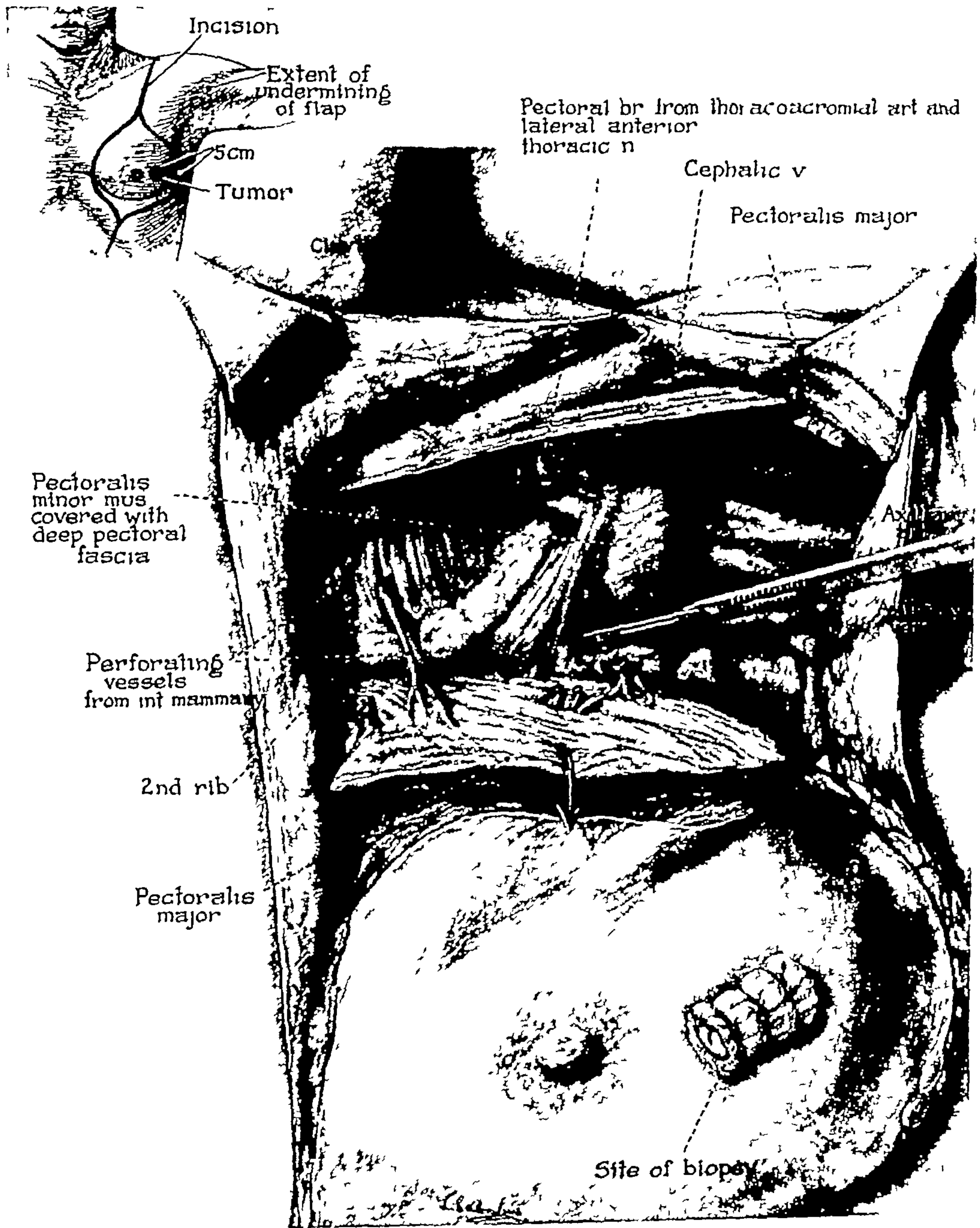


FIG 89 The skin flaps have been elevated and the pectoralis major muscle reflected downward partially uncovering the anterior wall of the axilla Insert reveals the tumor site, margins of incision and extent of undermining

portion of the pectoralis major muscle is to be left intact, the branch of the lateral anterior thoracic nerve which supplies this part of the muscle should be spared if possible

The pectoral branch of the thoraco-acromial artery, its accompanying vein and the lateral anterior thoracic nerve are isolated from their superficial position in the loose opaque fascia and areolar tissue on the surface of the pectoralis minor muscle This neurovascular bundle is traced back to near its axis or origin and carefully ligated The superior and lateral thoracic vessels vary in size and position but are usually found as they cross the operative field to enter the undersurface of the pectoralis major They should be carefully isolated and ligated before the body of the pectoralis major muscle is elevated from the chest wall

The dissection proceeds next to the sternal

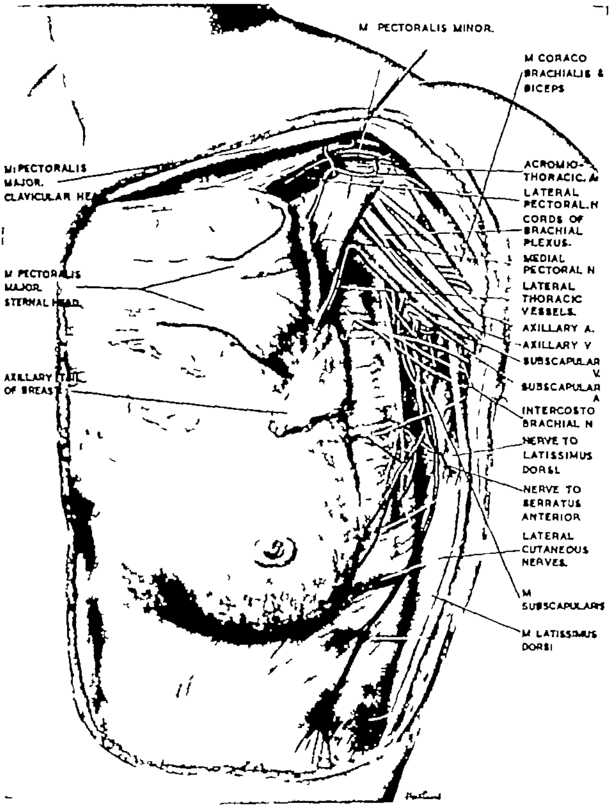
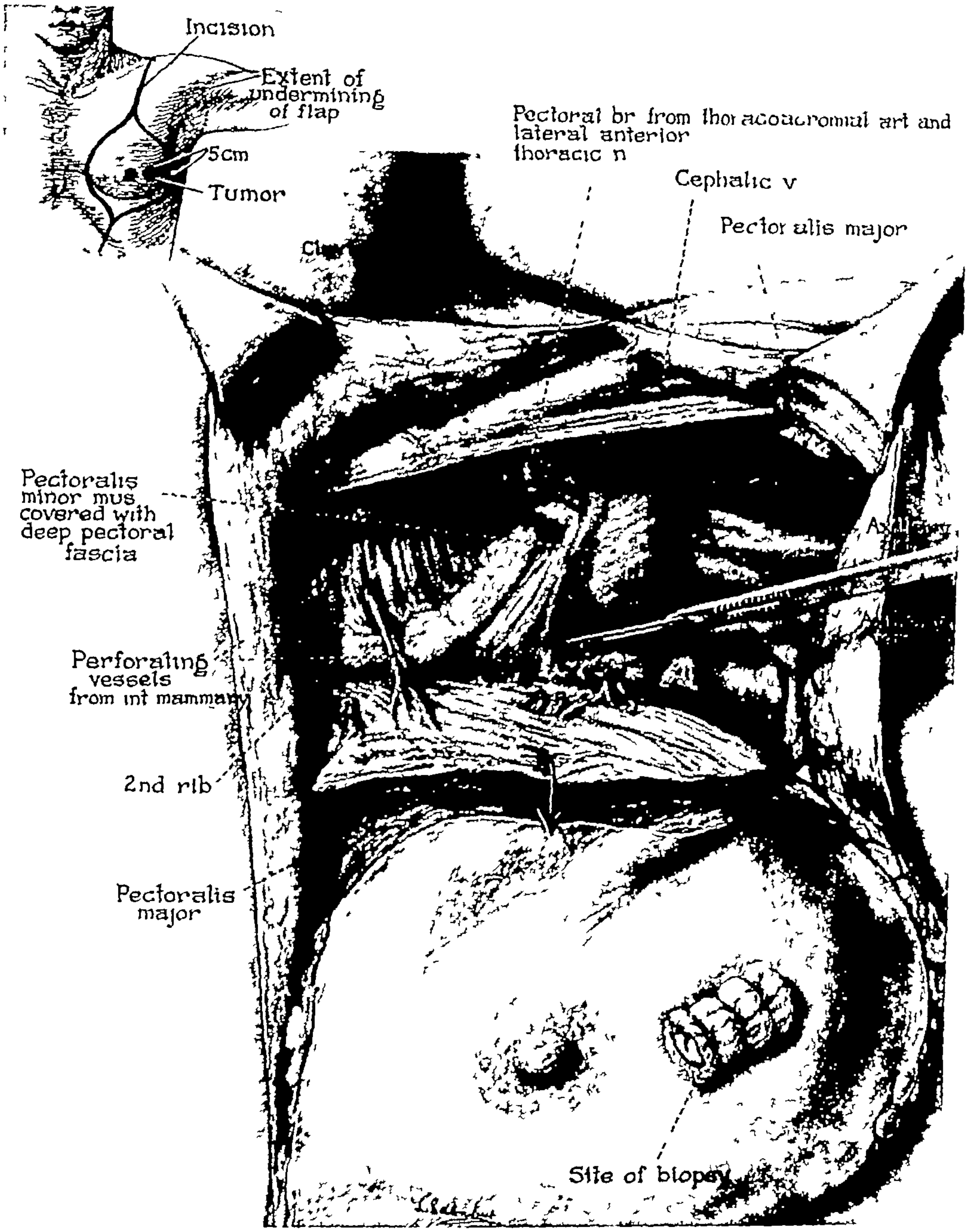


FIG 90 Partial reflection of the insertion of the sternal head of the pectoralis major muscle revealing the anatomical position of the underlying nerves and vessels to be encountered during the dissection (After Handley)



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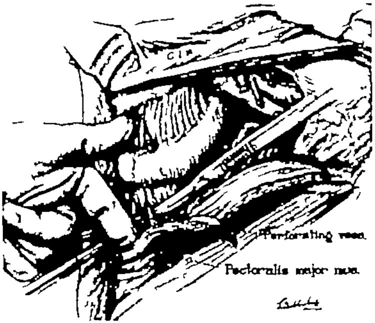

FIG 92 Placing an index finger beneath the sternal margin of the pectoralis major muscle facilitates the dissection of its sternal origin Blunt nosed hemostats secure the perforating vessels many of which can be seen before they are cut

attachment of the pectoralis major The separation between the clavicular and sterno-costal heads of the muscle is completed by finger dissection to the sterno-clavicular juncture A finger is passed beneath the attachment of the muscle and the fibers are severed by scalpel close to the upper part of their origin The medial margin of the upper interspaces is exposed as this dissection proceeds downward The upper *three or four intercostal spaces are fairly* wide at their medial ends, the second usually being the widest and containing the largest perforating vessels.

It is well to remember that the breast is generously supplied with arterial blood as evidenced for example by its profuse vascularity during pregnancy The perforating branches of the internal mammary artery provides the breast normally with the majority of its blood supply The internal mammary artery arises from the subclavian (see Chapter II) and descends behind the costal cartilages, very close to the edge of the sternum, to the level of the sixth interspace where it divides. The paired anterior perforating arteries run forward in the upper four interspaces through the intercostal muscles to enter the undersurface of the pectoralis major There are often two perforating arteries in each space, the upper of the pair being the larger The pair of perforating arteries in the second interspace is frequently of considerable size (fig 91)

The body of the pectoralis major is surgically excised from the chest wall at the sternum by placing the index finger in the space between the thoracic cage and the pectoral muscle With the muscle fibers held *under tension they are carefully severed from* their broad origin to the sternum and costal cartilages (fig 92)

The branches of the anterior perforating arteries should be identified and cleanly clamped as they are encountered Entering the deep surface of the pectoralis major many perforating vessels are encountered As the sternal origin of this muscle is detached some of these vessels hidden within the taut muscle fibers, can be secured only after they have been severed By inserting the index finger into the loose areolar space beneath the muscle, gentle traction may be exerted and blunt-nosed hemostats can be applied to those vessels which are visualized before they are cut. Sharp dissection should not proceed in a plane too close to the chest wall The hazard of vessel retraction is quite

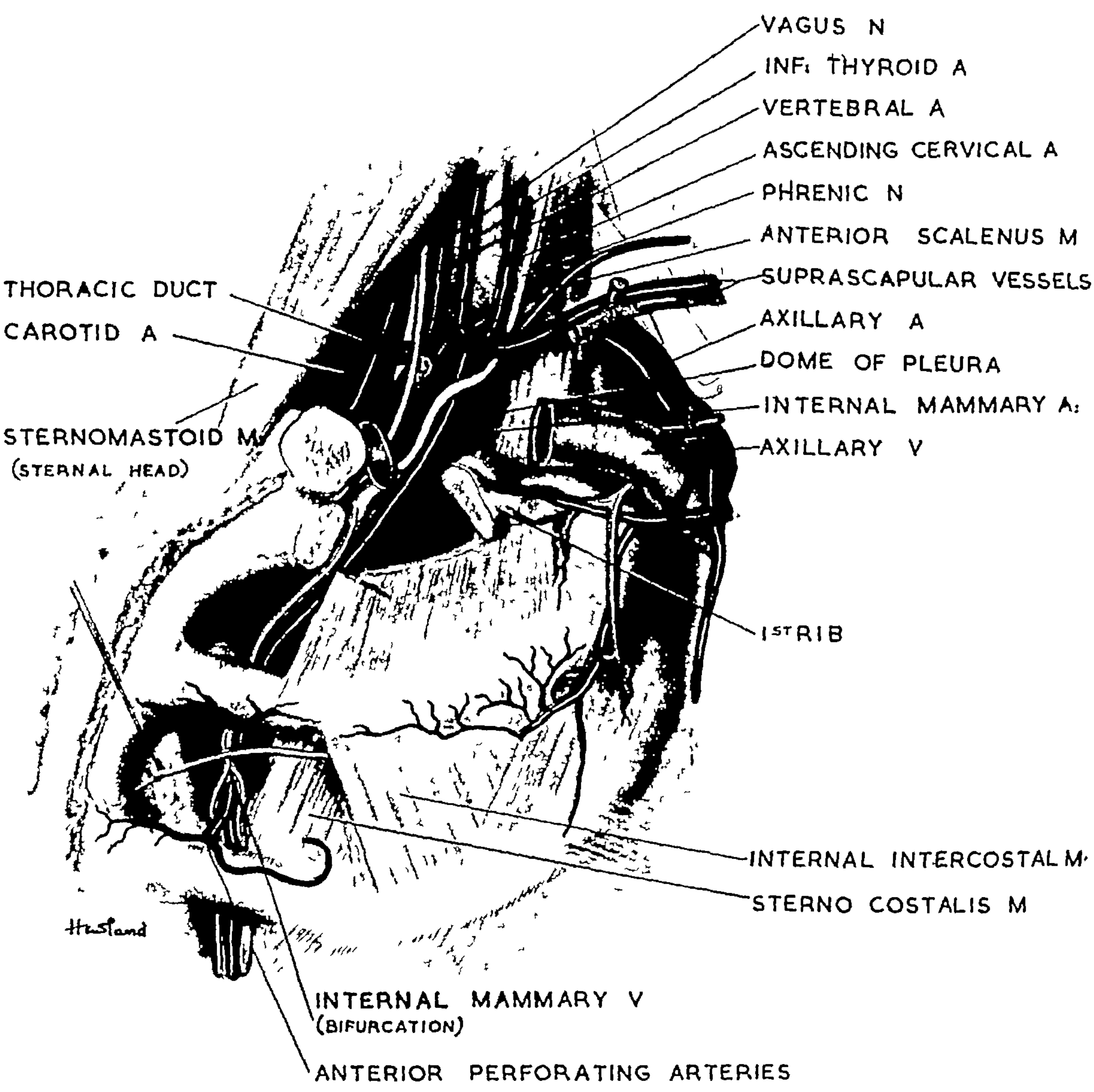

FIG 91 Showing the relationships between the anomalous origin of the internal mammary artery and its position adjacent to the sternum behind the ribs and intercostal muscles (After Handley)

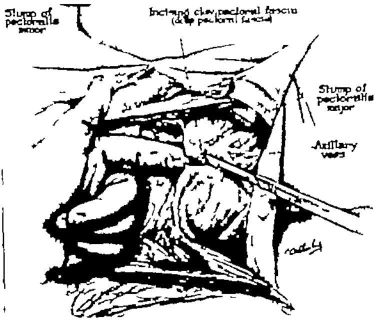

FIG 93 Incising the thickened lateral portion of the clavipectoral or deep pectoral fascia With the index finger protecting the underlying neurovascular bundle the fascia is severed by a slightly curved lateral incision

freed of its attachments to its point of origin from the anterior surface of the second third fourth and fifth ribs.

The slips of muscle are next severed by sharp dissection from their origin to the chest wall Careful dissection is required to avoid damage to the fibers of the serratus anterior with which the pectoralis minor interdigitates The breast its tumor and the underlying pectoral muscles now remain attached to the lower chest wall by the broad expanse of pectoralis major muscle origin at its inferior perimeter The axillary tail of the breast remains continuous in the upper and outer quadrant with the uncovered but undissected axillary contents. Without a change in position the force of gravity will carry the bulk of this tissue mass laterally off the chest wall

Dissection of the Axilla

Excision of the pectoralis minor from between the layers of the clavipectoral fascia often leaves a crescent shaped lateral edge of thickened fascia which overlies and crosses the neurovascular bundle This fascial sheath extends outward into the axilla where it encloses the nerves and vessels This fascia containing nerves vessels, fat areolar tissue and nodes must be removed to reveal the lateral axillary contents

The dissection of this axillary part of the clavipectoral or deep pectoral fascia is a most important but perhaps most confusing, part of the operation It is simplest to open this sheath by first inserting a finger beneath the fascia at its crescent-shaped edge (fig 93) This oval opening is at the site of the previous incision created through the lateral and lower part of the clavipectoral fascia and made to facilitate the removal of the pectoralis minor tendon The finger follows the course of the neurovascular bundle outward separating it carefully from the overlying fascial covering With the index finger in place protecting the underlying vessels the fascia is severed along the medial border of the corachobrachialis muscle (fig 93)

This incision then curves inward across the neurovascular bundle to finish at its medial margin This thickened and aponeurotic layer of clavipectoral fascia is now reflected downward to expose to its fullest extent the axillary contents

Dissection of the axilla now can proceed in either a medial or lateral direction. Some

real and may result in the necessity of ligating the internal mammary vessels to prevent serious hemorrhage This complication may needlessly prolong the operation The hemostats used are blunt-nosed and held parallel and not at right angles to the chest wall to prevent the accidental perforation of the thorax through the thin layer of intercostal musculature.

This part of the extensive excision of muscle can be most shocking if associated with excessive blood loss Care must be taken to insure prompt and meticulous hemostasis without undue damage to remaining muscle tissue Replacement of blood by transfusion begun prior to this stage of the operation is always desirable

Smaller branches of the intercostal vessels will perforate the interspaces in the midclavicular line of the anterior chest wall, and these are clamped and ligated as they are encountered

The excision of the pectoralis major muscle is carried down to its inferior attachment on the chest wall This is below the site of origin of the pectoralis minor muscle The upper four intercostal spaces are then carefully cleaned of areolar tissue, and all small bleeders are clamped The large denuded surface of the chest wall is covered with a warm, moist saline pack, and the next step in the procedure is to discontinue the dissection and consolidate the operation to the present stage All of the hemostats which have accumulated and which act as a heavy weight on the chest are now ligated or coagulated and removed Fine silk (4-0) ligatures are ordinarily used, but an occasional suture-ligature will be required for a perforating vessel lying flush with the intercostal muscles

Division of the Pectoralis Minor Muscle. As noted in Chapter II, the surgical key to the axilla is the clavipectoral (or deep pectoral) fascia and the pectoralis minor muscle which this fascia encloses between its two layers The medial and upward extension of this fascia is rather thin and frequently referred to as the costocoracoid membrane The lateral and lower extension of this fascia is tough and aponeurotic and continues outward to ensheath the neurovascular bundle and lateral axillary contents

Due to the difference in density of the clavipectoral fascia on either side of the muscle, a small incision is usually made first at the medial and upper margin of the pectoralis minor muscle (care being taken to avoid the underlying axillary vein), and a finger is easily introduced beneath the pectoralis tendon but above the axillary vein To allow the finger to emerge on the lateral and lower side of the tendon a small incision is again made, this time through the thick portion of the fascia

With the tendon of the pectoralis minor elevated and tented over the index finger, it is then sharply divided (between clamps is preferred but not necessary) close to the coracoid process Avulsion of the tendon is to be avoided because of deep bleeding Several small vessels are usually present in the tendon and should be carefully ligated to prevent persistent bleeding which will obscure the subsequent axillary dissection

The body of the muscle is then turned back from its insertion and the nerves and vessels entering its undersurface are now seen These are clamped, cut and ligated separately if possible The axillary vein which appears as a broad, flat, dark blue band crossing beneath the upper part of the muscle is now readily visible for the first time and easily identified In addition to the branches of the axillary artery and the medial anterior thoracic nerve which pierce the muscle, the lateral perforating vessels of the intercostal arteries send several branches which supply and wind around the edge of this muscle The entire muscle is carefully

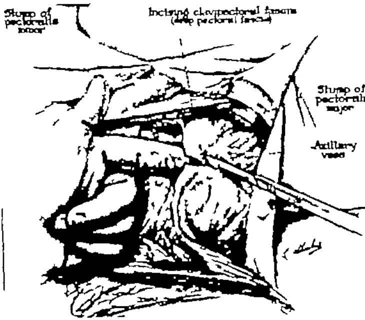

FIG 93 Incising the thickened lateral portion of the clavipectoral or deep pectoral fascia. With the index finger protecting the underlying neurovascular bundle the fascia is severed by a slightly curved lateral incision

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Dissection of the axilla now can proceed in either a medial or lateral direction Some

surgeons prefer to mobilize the distal portion of the axillary vein first. Here the venous tributaries are long and readily removed with little difficulty, thus allowing greater facility as one approaches the apex of the axilla where the dissection is more delicate.

However, most often the sequence of events in the orderly block dissection of the axilla is best begun at its apex which is so marked by a silk suture. This allows the surgical pathologist a better orientation in describing the number and site of node metastases. There is ample reason to believe that lymph node metastases which have reached the apex of the axilla have probably passed beyond. Thus, this point of pathological examination is a most important one in predicting the patient's prognosis. Embolic spread by local lymphatics to the axillary and internal mammary nodes is now a generally accepted concept. Although the breast is known to pour the major portion of its lymph drainage into the axilla, there is no certainty that all nodes of this chain will be involved in metastatic spread. Alternate routes to more remote nodes may be the course of metastases without affecting the intervening nodes.

The apex of the axilla is a small pyramidal space bounded above by the medial end of the clavicle, the clavicular head of the pectoralis major muscle and the subclavius muscle, below by the first rib and intercostal space and behind by the subclavian vein (the axillary vein becomes the subclavian at the border of the first rib). Several of the highest and perhaps most often overlooked but obviously important lymph nodes may be present at this point. Small veins which are quite fragile are frequently found in the summit of this space.

By a combination of sharp dissection with the scalpel (for the most part) and some gentle brushing with a moist gauze-covered finger, the axilla is methodically and carefully cleaned. Although this part of the axillary dissection can be accomplished more quickly by a blunt sweeping motion with a gauze-covered fingertip, the more meticulous but slower method of sharp scalpel dissection and gentle teasing of the areolar tissue is certainly to be preferred.

By the use of thumb forceps without teeth and a scalpel, the thin membranous part of the costocoracoid membrane at the apex of the axilla and the adjacent fat and areolar tissue (including small lentil-sized embedded lymph nodes) are cleanly dissected downward away from the wall of the vein which at this point has become the subclavian. Gentle retraction of the clavicular portion of the pectoralis major muscle may be required. The meticulous dissection of this area is essential for the complete removal of all possible lymph node metastases.

The mass of areolar and node-bearing tissue is removed from the level of the vein downwards, dissecting close to the vein and ligating all vessels immediately after clamping and cutting (fig. 94). Fine silk ligatures are immediately applied to prevent the clamps from being inadvertently torn away either by their own weight or by the manipulations of quick sponging of the operative field.

Complete and careful dissection of the entire vein from the apex of the axilla (where it first appears below the clavicle) to the point of its disappearance on the arm should be accomplished. All tributaries of the vein should be sacrificed. They are doubly clamped, cut and ligated close to the wall of the vein. In its lateral course the axillary vein may divide one or more times before entering the arm. It is best to preserve the axillary vein intact, but in cases of necessity it may be ligated without fear of serious consequences. However, the routine resection of the axillary vein as a part of the en bloc dissection of the axilla is an unnecessary

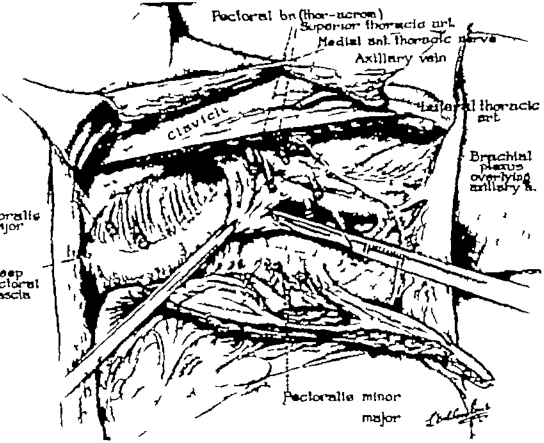

FIG 94 Dissection of the fat, lymph nodes and areolar tissue from the wall of the axillary vein The axilla has been exposed by division of the pectoralis minor muscle and the partial removal of the lateral (clavipectoral) and medial (costocoracoid) fascial coverings

procedure possibly adding to the likelihood of lymphedema

Many years ago however Halsted (22) observed that the excision of the axillary and supraclavicular glands plus resection of the subclavian and axillary vein is rarely followed by noticeable swelling of the arm. Even the occlusion of the axillary vein by recurrent tumors plus the excision of the axillary lymph nodes was not found by Halsted to give rise to lymphedema of the arm Trimble (62) has suggested that excision of the axillary vein was advisable in certain selected cases Sometimes the wall of the axillary vein is invaded by metastatic growth Should this be the case the vein should be resected without hesitation Experience has shown that no harm will result from this procedure not even postoperative edema of the arm An extensive review of this subject has been reported by Lobb and Harkins (33) (including the more radical recommendations of Macdonald (37)) and it is the opinion of these authors that segmental excision of the axillary vein caused little postoperative swelling of the arm (see Chapter XIII) Lobb and Harkins concluded that when indicated in order to remove adherent cancer containing lymph nodes the axillary vein should not be spared

Excessive handling and manipulation of lymph node-bearing tissue is to be carefully avoided Cancer cells are ever present and all possible contamination which has been repeatedly demonstrated by the cytologic examination of washings must be kept to a minimum.

The fat and areolar tissue lying *above*

the axillary vein in the region of the brachial plexus is seldom dissected unless there is an obvious lymph node in the area which can be readily removed Exposure of the axillary artery or the brachial plexus indicates that the plane of dissection is proceeding at a higher level than necessary All structures which cross the cleanly stripped vein from above are sacrificed

After the upper and anterior aspects of the vein have been carefully cleaned, its undersurface must be cleared to eliminate another important pocket of areolar tissue and node-bearing area This lies in the narrow cleft bounded above by the vein and below by the chest wall From this cleft emerge the thoracodorsal and long thoracic nerves which should be preserved

Dissection of the Lateral and Posterior Chest Wall

There now remains the completion of the chest wall dissection The previously dissected mass of tissue beginning below the vein at the apex of the axilla is continued in its removal in a downward and outward direction Containing fat, lymph nodes and loose areolar tissue, this dissection includes with it the layer of fascia covering the fasciculi of origin of the serratus anterior muscle

Several cutaneous branches of the intercostal nerves—namely, the intercostohumeral and intercostobrachial—traverse the axillary cleft from the upper intercostal spaces to the region of the lateral axilla and upper arm Because these nerves cross the axilla in such a manner as to prevent the en bloc dissection of the complete axillary contents, they are usually sacrificed Division and ligation is carried out close to the chest wall thus preventing the possible occurrence of a painful neuroma The division of these nerves results in a sensory loss over the skin of the upper and medial aspect of the upper arm

Deep in the cleft of the lateral chest wall in a plane posterior to the vein, lying in the loose areolar tissue beneath the fascia of the serratus anterior, will be seen the long thoracic nerve of Bell (fig 95) Its course is vertical along the lateral chest wall It is usually a simple matter to identify and dissect out this nerve, carefully releasing it without injury from its fascial covering Stripping the fibers of the serratus anterior of their fascia in this area may accidentally avulse the nerve as it supplies the digitations of this muscle Preservation of this nerve is considered prudent surgery unless it is grossly embedded in cancer tissue

The dissection is next carried down to the undersurface of the subscapularis muscle as it lies next to the posterior chest wall (fig 96) The axillary contents are dissected downward along with the thin layer of subscapular fascia This thin fascial sheath of the subscapularis and teres major is continuous at the base of the posterior cleft with the fascial covering of the chest wall

Running vertically outward and downward from behind the axillary vein is the thoracodorsal nerve which innervates the latissimus dorsi muscle This nerve lies in close proximity in its course to the subscapular vessels It is advisable to dissect the nerve free of its surrounding vascular attachments to prevent recurrent bleeding, and, if not involved grossly in tumor-bearing lymph nodes, the thoracodorsal nerve should be saved Although the division of this nerve causes no serious postoperative disability of the arm because of paralysis of the latissimus dorsi muscle, yet it should be spared whenever possible Isolation and high ligation of the accompanying subscapular vessels prevent hemorrhage, blind clamping and possible damage to the thoracodorsal nerve However, when nodes are grossly present along the course of the nerve or if it is em-

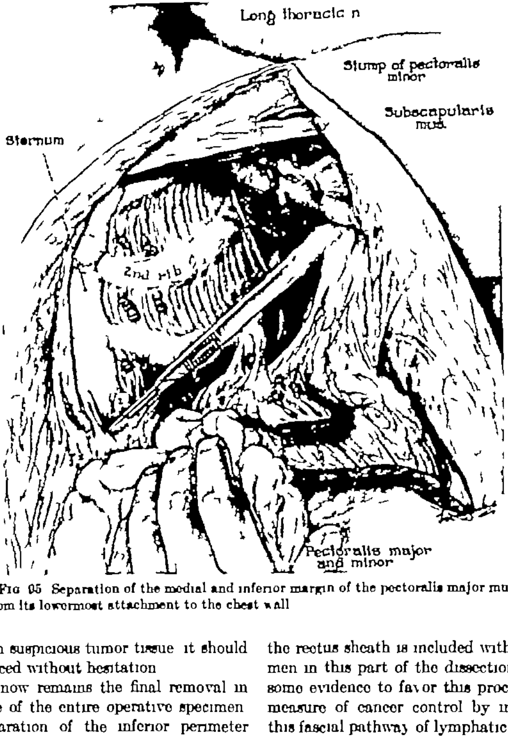

FIG 95 Separation of the medial and inferior margin of the pectoralis major muscle from its lowermost attachment to the chest wall

bedded in suspicious tumor tissue it should be sacrificed without hesitation

There now remains the final removal in one piece of the entire operative specimen The separation of the inferior perimeter begins at the medial margin of the lowermost attachment of the pectoralis major to the chest wall The muscle fibers are severed by sharp dissection and all perforating vessels are clamped cut and ligated In so doing the mass of tissue falls away laterally

If the malignant tumor is located in the lower hemisphere of the breast a segment of the rectus sheath is included with the specimen in this part of the dissection There is some evidence to favor this procedure as a measure of cancer control by interrupting this fascial pathway of lymphatic dissemination

Sharp dissection is used in separating the deep structures on the lateral chest wall and care must be taken to avoid dissecting the digitations of the serratus anterior as this can be easily done

The specimen is now freed of its final attachments which lie on the cleft between

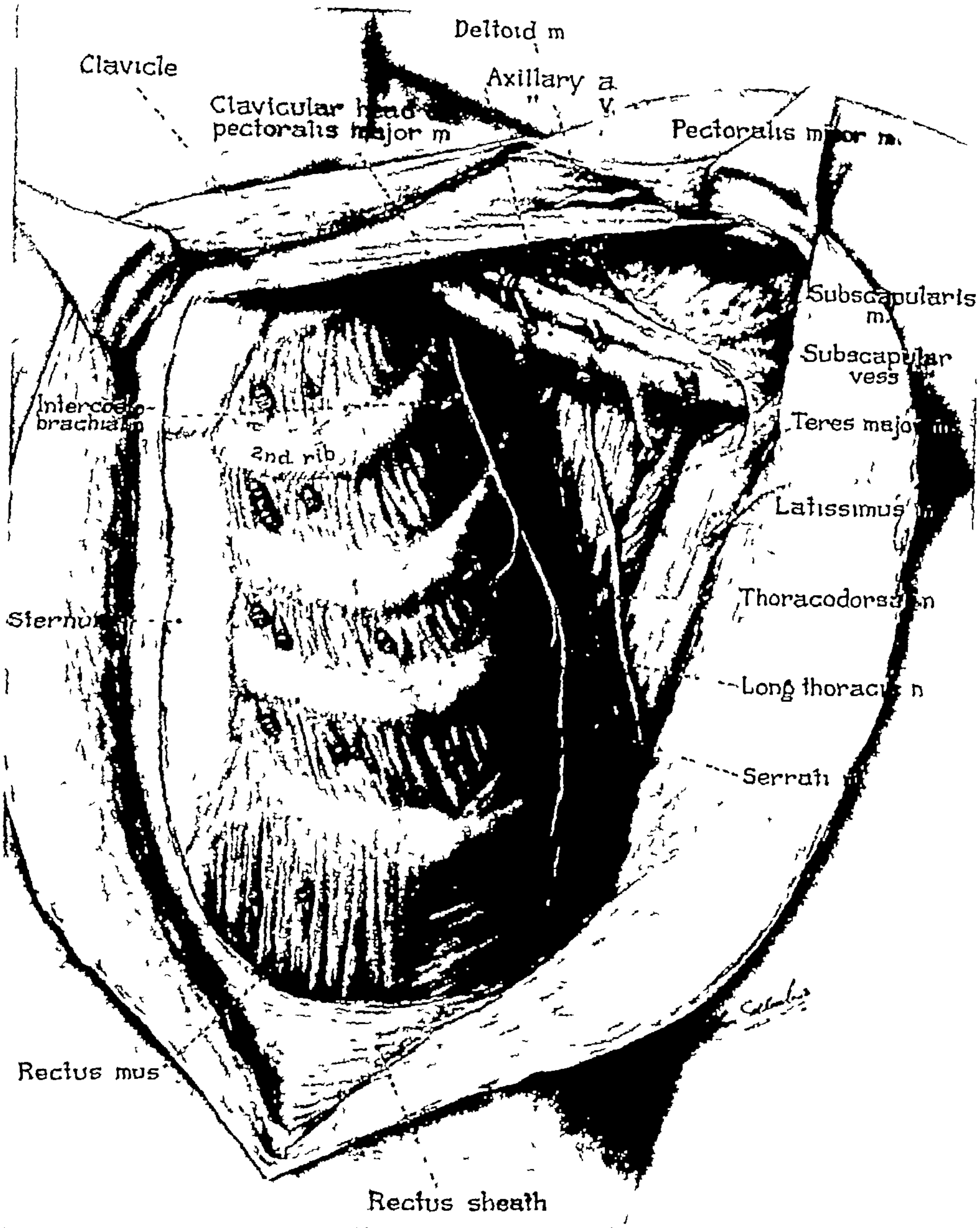

FIG 96 The operative specimen has been removed, and the anterior and lateral chest wall and axilla are completely exposed This demonstrates the relation of the long thoracic and thoracodorsal nerves (both of which have been preserved) to the axillary vein and the lateral chest wall

the chest wall and the previously defined latissimus dorsi muscle The dissection is carried from the chest wall outward toward the anterior edge of the muscle border Special attention at this stage is required to protect the thoracodorsal nerve as it enters the latissimus muscle, as well as the long thoracic nerve of Bell as it supplies the fasciculi of the serratus anterior

Deep in the cleft between the latissimus dorsi and the posterior-lateral chest wall lie the subscapular vessels which have been previously ligated However, injury to these vessels should be avoided as they are of considerable size and back-bleeding will be free The specimen is released at the border of the latissimus dorsi, and the entire breast, muscles and axillary contents finally are dissected completely free all in one piece

Closure

The entire operative area is now carefully inspected for small residual bleeders which are ligated with fine silk. A warm saline pack is used to cover the area and aid in hemostasis. If the patient's blood pressure has remained relatively constant during the course of the operation delayed bleeding should be no problem.

McGraw (36) has noted that, "wound closure after any long exacting operation is at best a tedious procedure that must be undertaken at a time when fatigue begets impatience and dulls judgment." However, in the matter of radical mastectomy, wound closure cannot follow a set routine. It should be approached as an exercise in plastic surgery, often requiring considerable surgical experience and decision.

The essential problem requires that the skin be reapplied to the chest wall 1) to provide covering for the axillary neurovascular bundle, 2) in such a manner so as to prevent serious skin slough from undue tension and 3) to preserve full function and a good range motion of the arm with a minimal amount of postoperative lymphedema.

The skin flaps are reapplied to the chest wall and sutured together first from above and then from below alternately. Interrupted fine silk sutures on curved French needles are used for approximation of the subcutaneous tissue. The skin is subsequently closed with interrupted silk sutures on fine straight needles (fig. 97). Retention sutures are never used because they further interfere with the blood supply of the skin.

Halsted in 1921 and several surgeons subsequently have advocated a type of skin closure designed to eliminate the infraclavicular and axillary dead-space thereby reducing fluid accumulation and the potential incidence of postoperative infection. The skin edge of the upper margin of the incision is

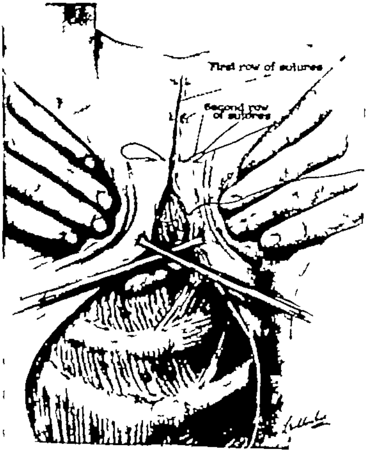

FIG. 97. Skin closure is performed using two layers of interrupted fine non absorbable sutures. Moderate traction by Allis clamps aided by the hand pressure of an assistant facilitates skin approximation.

sutured to the muscles of the first or second intercostal space This elevates the axillary fornix, minimizes fluid accumulation in this dead-space and prevents undue tension on the operative incision

Moore and Harkins (44) have suggested a technique for reconstruction and closure in cases of breast cancer which lie high in the axillary tail The latissimus dorsi muscle is utilized as a flap pedicle graft to cover and protect the axillary structures

Complete approximation of the skin edges under moderate but not excessive tension can usually be accomplished Skin flaps under severe tension may be an immediate cause of shock However, moderate traction by means of Allis clamps aided by skin approximation on each side of the incision by an assistant will greatly facilitate complete closure (fig 97) The surgeon must learn by clinical experience the margin of safety which is compatible with skin viability

Primary closure can usually be obtained in the majority of patients, but inability to bring the skin together is not a serious problem Either a primary or a delayed skin graft should secure prompt healing within a few weeks This may prove to be much sooner than a primary closure under tension which unfortunately develops a slough with subsequent delay and secondary closure

A primary skin graft (if required) is the procedure of choice However, any doubt as to the patient's ability to withstand prolonging the operation should preclude further surgery Final closure can be accomplished at a later time by means of a delayed graft

The edges of the defect to be grafted are sutured down to the chest wall, preferably in a central anterior position Primary closure over the axilla is always desirable The defect is covered with an intermediate or split thickness graft (the original type of Ollier-Thiersch graft was a very thin epidermal graft) taken from either the abdomen or the thigh The abdomen is preferred for cosmetic reasons The Padgett-Hood or Reese dermatome is used almost routinely, although small grafts may be cut by hand quite quickly by those experienced in the use of the Blair-Brown or similar knife In the case of delayed grafts either a split thickness dermatome graft or a number of small deep (Davis or Reverdin) pinch grafts can be used successfully at the end of about seven to 14 days There appears to be no uniformity of opinion regarding the best dressing for the grafted area Open and closed dressings have both been used successfully

Drainage. Although it is quite true that a certain number of these operative incisions can be safely closed without drainage, it has been our practice to drain all radical mastectomy wounds no matter how dry they may appear to be at the time of closure Regardless of faultless technique and excellent hemostasis most wounds tend to develop a lesser or greater accumulation of serum beneath the extensively undermined skin flaps This collection of fluid may be adequately treated by several postoperative aspirations if necessary, but, if neglected, the accumulated serum may distend the wound and seriously impair the blood supply of the flaps Repeated aspiration also favors the introduction of infection

A stab incision is made through the lateral flap well below the hair follicles and sweat glands of the axilla (fig 98) Prior to closure a split soft rubber tissue drain (Penrose drain without the gauze filler) is inserted in the wound One end of the drain extends upwards to the axilla but not sufficiently near the nerves or vessels to injure them, and the lower tail of the drain extends downward toward the flank and epigastrium The drain is usually withdrawn at the time of the first

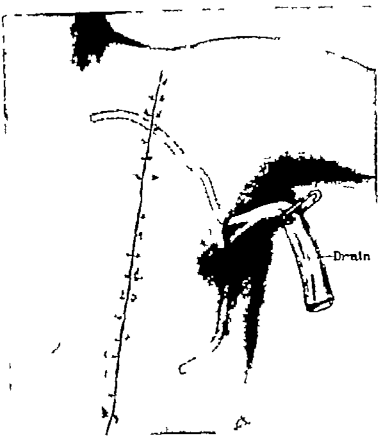

FIG 98 Drainage is usually carried out through a stab incision in the lateral flap well below the axillary sweat glands and hair follicles A split soft rubber tissue drain (Penrose drain without the gauze filler) is frequently used This is removed on about the fourth postoperative day

dressing on about the fourth postoperative day

Recently the use of negative pressure drainage has been described (45 51) for application under the skin flaps following radical mastectomy The procedure is simple requiring a number 16 20 or 24 French catheter semi-soft rubber or plastic tube with multiple openings which is inserted snugly into the lateral flap Negative pressure is applied by means of water or motor suction or a Wangensteen apparatus for the first 72 hours If skin grafting has been performed this method is contraindicated unless the drain is placed low in the lateral gutter The possible complications incident to the presence of a semi pliable open rubber tube must be determined by future experience but I have recently had occasion to see Handley at the Middlesex Hospital employ this method with excellent results and I have begun to favor its use in suitable cases

Dressings

The application of the initial dressing is an important part of the operative procedure The incision is first covered with a thin layer of xeroform or Vaseline gauze followed by a plentiful covering of sterile gauze over the entire operative area

The obliteration of the dead space in the axilla, as well as the obliteration of the normal concavity of the epigastrium and infraclavicular hollow is achieved by the use of an abundant amount of sterile mechanic s cotton waste This is held in place by large gauze pads. Negative pressure drainage may alter the need for positive pressure dressings

The patient is now ready to be slid upward until the upper half of the body is lying free of the operating table The body and the flail arm are firmly supported by several assistants while the adhesive elastic bandage is applied with considerable pressure (fig 99) The bandage is applied from one side of the chest across the operative area to the

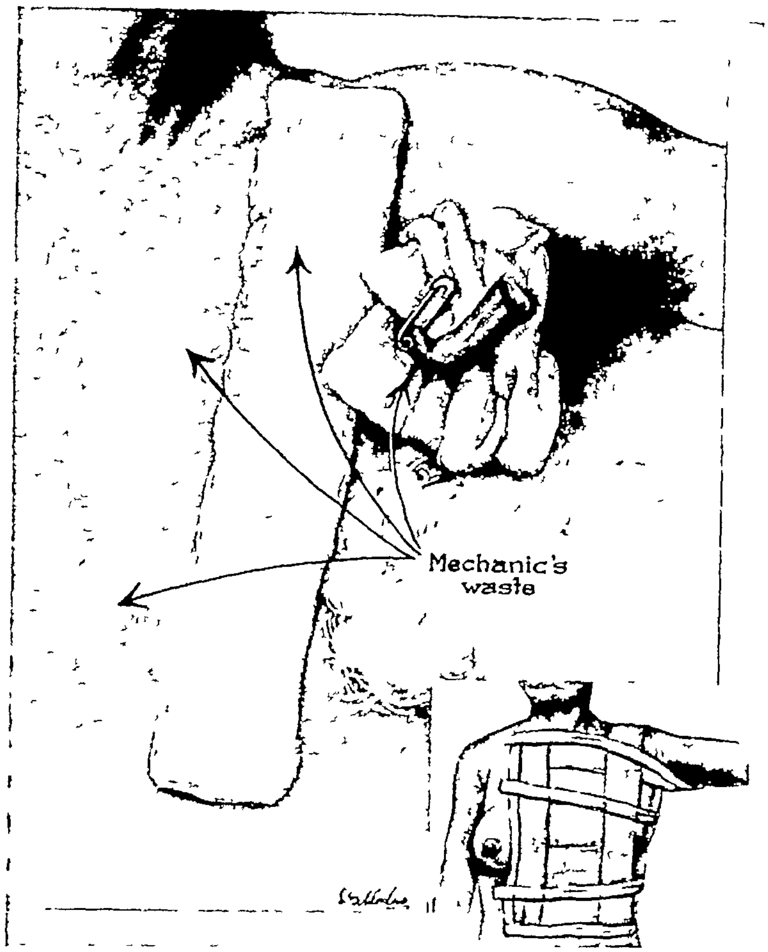

Fig 99 Dressings are designed to help obliterate (with cotton mechanic's waste) the dead space in the infraclavicular "hollow", axilla and epigastrium The insert shows the elastic adhesive bandage applied to the operative area without encasing the entire chest

posterior side of the chest without completely encasing the thorax The edges are bound down with strips of regular adhesive firmly applied Except for a single strap running over the shoulder the arm is free An arm sling may be used for early ambulation if desired, but it is best not to bind the arm down and to encourage use but not abuse at an early time

Special chest binders providing firm pressure and comfortable shoulder straps have been designed and used by some surgeons However, tight binders which completely encase the chest wall act as a constricting girdle preventing proper respiratory function

Parker, Russo and Oesterreicher (49) have recommended the use of a continuous compression bandage to the arm for a postoperative period of eight weeks This routine prophylactic bandaging of the arm is considered by these authors to be a satisfactory measure of lymphedema prevention This subject is discussed in detail in a following chapter (see Chapter XIII)

Simple Mastectomy

Clinical Indications for Simple Mastectomy

Many years ago, Bloodgood pointedly remarked that a simple mastectomy was too radical a procedure for benign breast disease and too conservative a procedure for malignant breast disease Although "no epigram contains the whole truth," the meaning behind this sage advice is more than a mere provocative half-truth

As suggested by Slaughter and Peterson (57), the operation of simple mastectomy may be performed as either a therapeutic or prophylactic procedure but should rarely, if ever, be performed as a diagnostic pro-

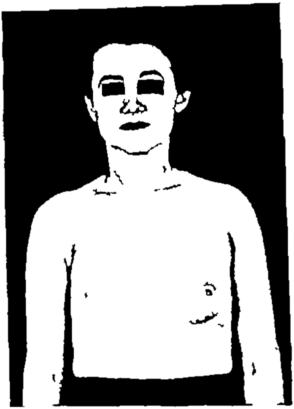

Fig 100

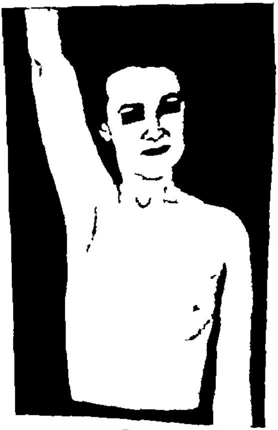

Fig. 1 1

consideration must be given each patient

- E Definitive treatment for the operable patient with breast cancer who is to receive postoperative radiotherapy in accord with the treatment technique of McWhirter The indications for this type of treatment policy depend upon the convictions of the surgeon and radiotherapist
- F Sarcoma of the breast
- G Extensive chronic suppurative lesions of the breast which fail to respond to chemotherapy
- H Exceptional cases of severe mastodynia which have failed to respond to conservative treatment

II Prophylactic simple mastectomy

- A Multiple or diffuse benign breast tumors with distinct premalignant potentials
  - 1 Multiple intracystic or intraductal papillomatosis
  - 2. Chronic cystic mastitis with diffuse and atypical epithelial hyperplasia
  - 3 Cystosarcoma phyllodes
- B Recurrent benign breast tumors
  - 1 Multiple, recurrent fibroadenomas or chronic cystic mastitis
  - 2 Cystosarcoma phyllodes

When simple mastectomy is performed without adequate justification, it is usually the result of surgical over-cautiousness and not a matter of poor judgment Prudent surgery is based upon the premise of safety first *However, in most cases where simple mastectomy has been performed for benign breast disease, simple excision of the tumor would have certainly sufficed* The mutilation associated with amputation or simple mastectomy in place of simple excision in the case of a young and attractive woman may precipitate serious psychic trauma and life-long psychologic disturbances

Simple mastectomy performed for uncomplicated benign breast disease purely as a measure of prophylaxis against subsequent cancer (see Chapter VI) is neither justifiable nor recommended. Simple mastectomy as a prophylactic adjunct to radical mastectomy performed on the opposite side has been seriously advocated by as distinguished a surgeon as Pack (48) and others This unique proposal is based upon the belief that breast cancer is of multicentric origin and should be treated by bilateral mastectomy (see Chapter XIX) Although "severity is allowable where gentleness is in vain", my own forbearance would spare the patients this routine ruthlessness

The increasing importance of geriatric surgery has given simple mastectomy a significant role in the treatment of the aged and infirm poor-risk patient It is usually advisable to administer radiotherapy following this type of simple surgery for breast cancer The study of Byrd (9) indicates that simple mastectomy offers these elderly and "categorically inoperable" patients a comfortable and almost complete fulfillment of their life expectancy

Lockhart and Ackerman (34) reported a carefully studied group of forty-one patients with proved breast cancer who had a simple mastectomy or local excision of their tumor performed prior to their admission for radical surgery The undesirable results which followed the use of simple mastectomy performed for diagnostic purposes were obvious These authors raise the question whether radical mastectomy performed secondary to simple mastectomy may not actually hasten the death of the patient It is my belief that in those cases developing local recurrence after simple mastectomy, radical mastectomy is never indicated Radiotherapy, local surgery, castration and hormone ther-

apy are effective palliative measures of equal benefit

Simple mastectomy is never indicated as a diagnostic procedure for operable breast cancer Persistent carcinoma as clearly demonstrated by the studies of Lockhart and Ackerman "almost invariably remains hidden in the operative field and/or axilla."

Surgical Treatment of Breast Sarcoma

Whereas the total number of breast sarcomas constitute only one per cent or less of all breast malignancies surgical interest and curiosity in the pathologic variation of this disease is great By the classification of Cheatle and Cutler (10) they are commonly divided into the adenosarcomas and the 'pure fibrosarcomas The adenosarcomas contain glandular elements in a sarcomatous stroma These tumors probably arise from fibroadenomas The "pure fibrosarcomas may arise from any of the mesenchymal tissues within the parenchyma of the breast (see Chapter V)

There is no unanimity of opinion regarding the preferred type of treatment for breast sarcoma A certain degree of this confusion is understandable and due to the rarity of the disease even in the personal experience of those interested investigators working at large surgical centers There appears to be no agreement among authorities as to which type of sarcoma carries the poorest prognosis or which is more malignant ' fibrosarcoma or adenosarcoma.

Practically all observers are in accord however that sarcomas of the breast rarely metastasize to the axillary nodes Adair and Hermann (3) found axillary involvement in only four per cent of 100 cases in which the lymph nodes were pathologically examined These four patients quickly succumbed to the disease Therefore it is generally considered the accepted practice to perform only a simple mastectomy with a block dissection of the pectoral fascia for this disease Removal of axillary nodes which are already the site of metastatic spread apparently does not improve the prognosis. In the collected series of Adair and Hermann the five-year survival rates for patients treated by radical mastectomy and those treated by simple mastectomy were almost identical

However Treves and Sunderland (61) writing from the same hospital as Adair and Hermann express a contrary point of view, at least regarding sarcomatous changes occurring in cystosarcoma phyllodes. "Malignant cystosarcoma phyllodes should be treated by radical mastectomy Though the mode of dissemination in this tumor is more often by way of the blood vessels than the lymphatics and though sarcoma of the breast metastasizes to the axillary lymph nodes in not more than four per cent of the cases, the complete operation appears to be indicated ' Some surgeons advocate extended simple mastectomy rather than radical mastectomy for a limited dissection of accessible axillary nodes.

The prognosis appears to depend mainly upon the histologic grade of the tumor according to Massie and McClellan (41) rather than upon the pathologic variety of the sarcoma. Local recurrences may be observed not infrequently and these must be treated energetically by means of repeated local excisions and/or radiotherapy if indicated

The over all five year survival rate for sarcomas of the breast varies considerably but, in general the prognosis appears to be somewhat better than for carcinoma of the breast Reliable statistics of large series are difficult to discover in published reports

Although it is perhaps the more common practice in dealing with breast sarcoma to perform a simple mastectomy with removal of the underlying pectoral fascia, yet when the axillary nodes are clinically enlarged an

extended simple mastectomy will allow adequate biopsy and frozen section diagnosis of the accessible nodes. If metastases are then found to be definitely present, the operative procedure should give the patient the benefit of the doubt and a radical mastectomy be performed

General Objectives of Simple Mastectomy

Before any description of the operative technique is undertaken, it is well to define the objectives of simple mastectomy As usually regarded, simple mastectomy includes the excision of the breast including the nipple and areola but not including the pectoral muscles or the axillary contents Ordinarily, the skin removal includes little more than the pendulous portion of the breast

However, as demonstrated by many observers, this standard technique of simple mastectomy is actually only a partial mastectomy The breast tissue extends far more widely over the chest wall than is the idealized impression Hicken (26), in a clinical pathologic study, has shown that complete dissection of the breast parenchyma is seldom accomplished by the routine type of simple mastectomy In 95 per cent of the breasts studied, the mammary ducts ascended into the axillary tail and some even extended along the vessels to the apex of the axilla In 15 per cent of the cases ductal breast tissue was also found in the epigastrium

Breast parenchyma is in close contact with the skin, frequently crosses the mid-line, passes posterior to the border of the latissimus dorsi muscle and extends well down on to the abdominal wall Thus, it is apparent that most simple mastectomy operations are only partial or incomplete resections This is clinically evident by the recurrence of benign or malignant tumors in an area previously operated upon for benign breast disease by simple mastectomy It is particularly unfortunate to find a breast cancer which develops in the axillary extension of the breast after a standard so-called simple mastectomy. Also, it is not at all uncommon to find patients with persistent premenstrual engorgement and mastodynia on the side of a previous simple mastectomy indicating the presence of residual breast tissue

Therefore, when simple mastectomy is to be performed for clinical conditions which do not require intensive postoperative radiotherapy, the subcutaneous dissection should be extensive and the excision of breast tissue as complete as possible Moderate amounts of postoperative radiotherapy will be tolerated by thin flaps However, if the radiotherapeutic principles of McWhirter are to be conformed to, then a wide dissection must *not* be performed The McWhirter treatment policy requires the most conservative type of simple mastectomy An extended local excision may best define this surgical procedure This precaution is required because (1) extensive skin flaps do not tolerate the large amounts of radiotherapy administered by this technique, (2) the field of therapy and the dose must be unrestricted and adequate, and (3) the incidence of lymphedema of the arm is greatly increased if intensive radiotherapy is combined with extended simple mastectomy or radical mastectomy A review of the results of the McWhirter technique and a discussion of its rationale will be found on pages 235–238

Operative Technique for Simple Mastectomy

The incision in simple mastectomy can be either a transverse or vertical ellipse (fig 102) which should be ample and made in accord with cosmetic considerations To reach the axillary tail by means of a transverse incision, it must be adequate in length,

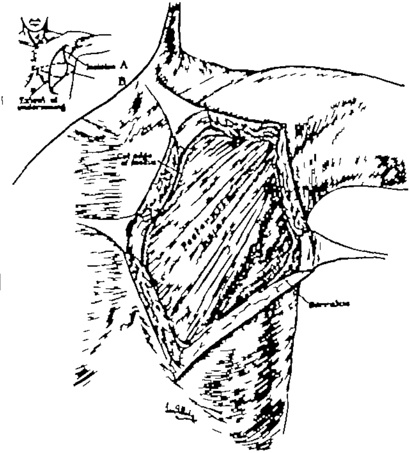

FIG 102 Simple mastectomy may be performed through either a transverse or oblique vertical incision The breast area is widely excised and the pectoral fascia is included in the dissection Skin flaps are actually much thinner than they appear

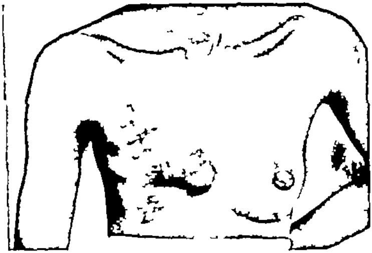

FIG 103 This patient with a prominent family history of breast cancer was operated upon seven times for recurrent cystosarcoma phyllodes A simple mastectomy was performed only to have the disease recur in adjacent remaining breast tissue

well undermined and readily retracted The nipple and areola are always included except in the use of a submammary incision (described by Thomas in 1882) or in the performance of a subcutaneous mastectomy

The skin flap is undermined in accord with the clinical condition and the objective of the operation For the most part a thin flap is extensively elevated over the breast area to assure thorough excision of mammary tissue (fig 102) I have personally observed one clinic patient with cystosarcoma phyllodes who had undergone seven local operations in 12 years for this recurrent breast disease the last three operations followed an inadequate simple mastectomy (fig 103) This

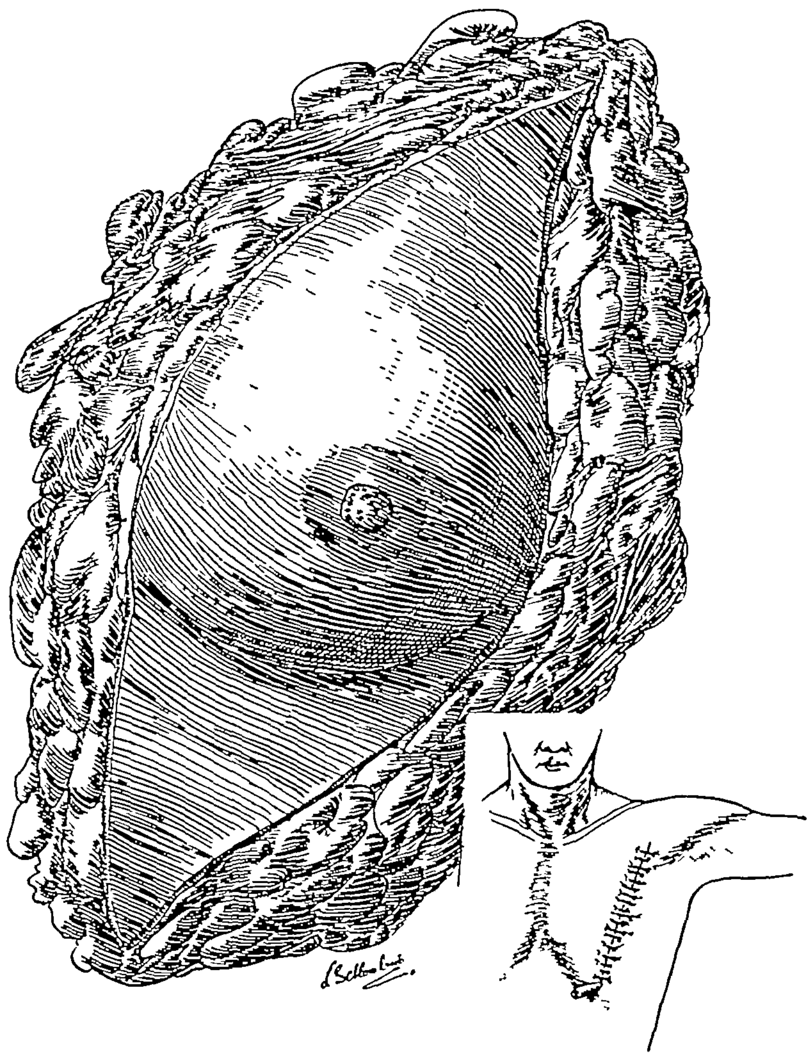

FIG 104 The operative specimen in a simple mastectomy should include as much underlying breast tissue as possible in addition to a generous ellipse of skin

may be the result of leaving behind lobules of target-organ breast tissue

Complete hemostasis is secured with fine silk ligatures In cases of malignant or even so-called "borderline" breast tumors, it is desirable to excise by sharp dissection the pectoral fascia lying on the anterior surface of the pectoralis major muscle This can best be done if the incision is vertical or in the axis of the anterior axillary line Scars within the axilla are to be carefully avoided In all cases of malignancy, dissection in continuity or en bloc dissection of the breast and pectoral fascia is preferred

Excision of the lowermost axillary nodes, when added to simple mastectomy, is known as an extended simple mastectomy By passing a finger along the axillary tail these nodes can be examined by palpation If enlarged firm nodes are encountered, they can be excised for examination and frozen-section diagnosis This procedure is particularly helpful in the case of sarcoma or cystosarcoma phyllodes Should the nodes reveal the presence of metastases, radical mastectomy may then become the operation of choice Although sarcoma of the breast infrequently metastasizes to the regional nodes, axillary metastases have been found to be present on rare occasions

Wound closure is similar to that described for radical mastectomy Skin grafting is almost never needed and a small rubber wick or Penrose drain can be inserted at the distal end of the incision if required (fig 104)

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CHAPTER XII

Extended Radical Mastectomy

JEROME A. URBAN, M.D

Surgical Extension of Radical Mastectomy

The prime objective of radical cancer surgery is the en bloc excision of the primary cancer together with its regional lymphatic drainage depots before distant metastases have occurred Early diagnosis followed by earlier and more radical surgery should increase the salvage rate of breast cancer provided the more extensive procedure is not accompanied by an increase in the post operative morbidity and mortality

With few exceptions the ancient surgeons treated breast cancer only after the tumor had extended widely and then only with minimal local surgical excision (see Chapter I) The modern concept of radical surgical therapy of breast cancer can be stated to date from 1867 when Charles H Moore, a surgeon at the Middlesex Hospital in London wrote an excellent article on "The Influence of Inadequate Operations on the Therapy of Cancer In this important contribution he maintained that mammary cancer requires the careful extirpation of the entire organ diseased axillary nodes should be taken away together with the breast without dividing the intervening lymphatics (and) a wide skin excision is important He also believed that the worse prognosis occurs when the primary lesion is situated next to the sternum"

The actual development of the radical surgical treatment for breast cancer began in 1894 when William Halsted and Willy Meyer both independently published a description of the procedure which we now recognize as the classical radical mastectomy (see Chapter I) Two main principles were stressed 1) removal of all of the pectoralis muscle with the exception of the clavicular portion so as to facilitate removal of all tissues in the axilla and 2) the resection in continuity of the primary tumor together with its lymphatic metastases to the axillary lymph nodes Halsted in 1898 (8) advocated further extension of the radical mastectomy procedure to include dissection in continuity of the supraclavicular region However follow up did not indicate any increase in the survival rate following this more extensive procedure and thus together with the increased operative mortality led to the abandonment of this particular extension of the radical mastectomy

At present the generally accepted treatment for primary operable breast cancer is the classical radical mastectomy procedure The five year survival rate with this form of therapy has increased from the figure quoted by Halsted (1907) and his co-workers, a 28 9 per cent five year survival rate to the present range of approximately 50 per cent five year survival rate as reported by several of

TABLE 42

Survival Rates in Primary Operable Cases Undergoing Radical Mastectomy at Memorial Hospital

	Overall Survival	Axillary Nodes −	Axillary Nodes +
	%	%	%
5 yr (3,495 cases) 97 8% follow up	54 4	77 5	39 4
10 yr (1,668 cases) 94 6% follow up	33 8	53 8	21 2

Overall five- and ten-year survival figures following routine radical mastectomy with postoperative X-ray therapy

the large clinical centers (see Chapter X) The principal reason for this improvement has not been due to any increase in radical surgical technique but rather to the earlier detection and treatment of breast cancer—treating the lesion before it has become disseminated Nevertheless, despite earlier diagnosis, there remains a mortality rate of 50 per cent in cases of primary operable breast cancer within the first five years The most recent figures quoted from Memorial Hospital in New York City showed a five year over-all survival rate in a series of 3,495 cases treated by radical mastectomy as 54 4 per cent (Table 42) This data revealed a 77 5 per cent five year survival rate for the cases with negative axillary nodes and a 39 4 per cent five year survival rate for those cases with positive axillary nodes The ten year survival rate for the over-all group was 33 8 per cent Certainly there is no room for complacency and self-satisfaction with these results of radical mastectomy for primary operable breast cancer

During the last 25 years several procedures have been devised to extend the radical mastectomy operation In 1927, William Sampson Handley (9) advocated routine insertion of radon tubes into the parasternal interspaces in order to control the spread of breast cancer into the internal mammary lymph nodes Apparently this plan did not succeed too well since it was eventually abandoned He also mentioned that in several instances the internal mammary nodes had been removed through the interspaces following the completion of radical mastectomy More recently other investigators have extended the scope of the radical mastectomy procedure in an effort to increase the salvage rate of primary operable breast cancer Owen Wangensteen at the University of Minnesota has devised a procedure which includes the conventional radical mastectomy and axillary dissection, dissection of the supraclavicular space up to the upper border of the thyroid cartilage, resection of the internal mammary chain from the fifth intercostal space to the subclavian blood vessels and a dissection of the anterior mediastinum along the innominate veins This procedure is not an en bloc procedure but rather is performed in separate steps without preserving continuity between the primary tumor and the lymph node depots in the base of the neck and the internal mammary chain In a group of patients subjected to this procedure (a large number of whom had extensive disease) approximately 60 per cent have been shown to have metastases in nodes which would not have been removed by the radical mastectomy procedure Unfortunately, the operative mortality rate with this procedure has been considerable

For several years Professor Mario Margottini (13) of Rome has exposed the internal mammary chain nodes following radical mastectomy by incising and retracting the cut margins of the second, third, and fourth costal cartilages and has then removed the internal mammary chain of nodes from the first to the fifth ribs together with the internal mammary blood vessels By 1951 a series of 192 cases had been done and 22

per cent showed positive internal mammary nodes In a smaller group of patients who had involved axillary or internal mammary nodes a supraclavicular dissection was done with the finding of 20 per cent positive neck nodes In Copenhagen Professor Dahl Iverson (4) has extended the radical mastectomy operation to include a supraclavicular dissection as well as a dissection of the internal mammary nodes. He likewise does not perform an operation in continuity A radical mastectomy is first performed and then the supraclavicular dissection follows The internal mammary nodes are excised by resecting portions of the costal cartilages and removing the internal mammary nodes together with the internal mammary vessels extrapleurally Clarence E Gardener at Duke University has included an internal mammary dissection as well as supraclavicular dissection in a small group of patients

While these surgeons were advocating the more radical surgical treatment of breast cancer Professor Robert McWhirter (16) of Edinburgh had developed his own conservative technique of treatment consisting of simple mastectomy followed by early intensive postoperative X ray therapy (see Chapter XI) This is aimed particularly at the node-bearing areas in the axilla neck and internal mammary regions In primary operable breast cancer he believes that he has increased the survival rate over the survival rate previously obtained with radical mastectomy

In considering extension of the radical mastectomy procedure for breast cancer I have been impressed with the following important factors 1) the necessity of removing all of the primary lymphatic drainage area together and in continuity with, the primary breast cancer 2) the need for early diagnosis and early radical surgical therapy before the disease has spread beyond the primary regional lymphatics

The primary lymphatic drainage of the breast extends into two main primary depots, the axillary lymph nodes and the internal mammary lymph node chain In order to encompass both of these primary pathways of lymphatic drainage from the breast we have devised an original procedure for removing the internal mammary lymph node chain en bloc in continuity with radical mastectomy Other primary routes which are less frequently involved are the intercostal lymphatics and primary hematagenous route of spread In the great majority of cases which spread to the axillary or internal mammary nodes secondary drainage then extends to the nodes in the base of the neck Here the lymphatic vessels drain into the venous system at the confluence of the internal jugular and subclavian veins When cancer cells enter this junction, the disease becomes systemic and beyond the scope of extirpative surgery

The primary lymphatic drainage of the breast has been described by many anatomists W C Cruikshank as early as 1790 described the lymphatic drainage of the breast as draining into two primary depots, the axillary and the internal mammary chain of nodes Most of our standard textbooks of anatomy have demonstrated the importance of the internal mammary drainage from the breast for many years Stibbe (18) in 1918 at the suggestion of William Sampson Handley investigated the anatomy of the internal mammary lymph node chain and outlined the usual pattern of distribution of these nodes He demonstrated their relative frequency in the first, second and third intercostal spaces and showed that they were found much less frequently in the fourth and fifth interspaces Rouviere (17) in his classic description of the human lymphatic system traced the lymphatic drainage of the breast into two primary depots the axillary and internal mammary chain From these depots

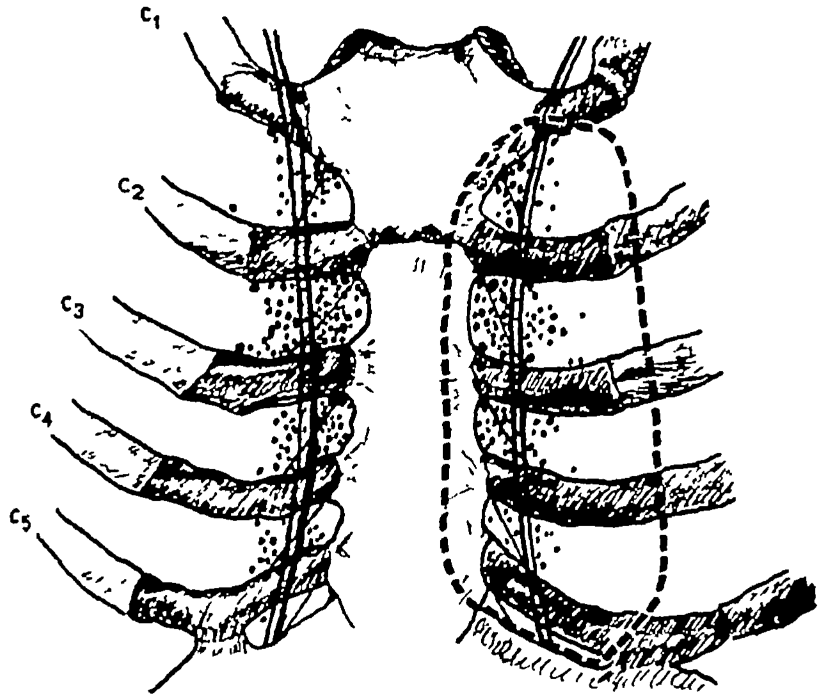


FIG 105 Location of internal mammary lymph nodes as found by Andreassen, Dahl-Iversen and Sorensen The dotted line superimposed over the photograph designates the usual limits of the chest wall excision in our operative procedure In order to remove the lymph node bearing area adequately it is obvious that a portion of the sternum must be included in the en bloc excision

secondary drainage extends mainly into the lymph nodes at the base of the neck and into the jugulo-subclavian venous junction

Richard S Handley (10) has most dramatically demonstrated the surgical importance of the internal mammary lymph node chain in primary operable cancer of the breast (see Chapter II) In his first series of 100 primary operable breast cancers in which the internal mammary nodes were biopsied during radical mastectomy, he found cancer-bearing nodes in the internal mammary chain in approximately 60 per cent of the medial half lesions and about 20 per cent of the lateral half lesions Handley also found viable-appearing cancer cells in the internal mammary nodes of three out of five cases which were explored after having received intensive X-ray therapy More recently, in 1954, Andreassen, Dahl-Iversen and Sorensen (2) in a series of 100 primary operable breast cancers in which radical mastectomy was extended to include a low neck dissection and excision of the internal mammary nodes, demonstrated involvement of the nodes in the various depots (table 44) In this series of 100 primary operable cases, 55 per cent showed no metastases in any nodes Forty-one per cent showed positive axillary nodes, 17 per cent showed positive internal mammary nodes and only three per cent showed positive supraclavicular nodes When the axilla was positive, seven per cent showed positive supraclavicular nodes and 32 per cent had positive internal mammary nodes. When the axilla was negative, no supraclavicular nodes were involved, while eight per cent had positive internal mammary nodes

Stimulated by the work of Maier who re-

TABLE 43

Invasion of Internal Mammary Lymph Nodes in Breast Cancer

	Inner Half	Outer Half	Total
All nodes (−)	16	33	49
Axilla (+)	12	40	52
Internal mammary (+)	6	2	8
Both (+)	27	14	41
Total	61	89	150

Handley and Thackeray, 1954

Results of internal mammary biopsy at time of radical mastectomy for primary operable breast cancer

ported a series of cases of radio-necrosis of the chest wall treated by radical full thickness excision with simultaneous closure by utilization of the opposite breast as a flap pedicle graft, in 1948 we decided to apply the same technique to postradical mastectomy cases presenting local chest wall recurrence in the absence of clinically evident systemic spread Under the direction and with the encouragement of Dr Frank E Adair, then chief of the breast service at Memorial Hospital this project now includes 28 cases In 11 instances widespread disease was noted in the intrathoracic organs despite negative roentgenograms physical and laboratory examinations Of the remaining 17 cases who grossly appeared free of intrathoracic metastases at the time of surgery, 12 are now living, having survived six months to six years following the secondary operation Two of these patients have further disease, and ten are clinically free of disease Seventy per cent of the chest wall recurrences were parasternal and undoubtedly represented overgrowth of an internal mammary node metastasis! A technique of closure utilizing fascia lata sutured into the chest wall defect under tension plus immediate closure with a full thickness sliding flap pedicle of skin and subcutaneous fat was found to be most satisfactory Paradoxical motion was minimized and often completely prevented by the tense fascia lata graft which occluded the defect of the chest wall. No appreciable discomfort or disability was caused by this closure It very soon became evident that one could by utilizing this technique combine this procedure with radical mastectomy and thus effect a primary removal of the original breast cancer together with an en bloc excision of both of the main primary lymphatic drainage depots of the breast

In deciding where to limit the extension of radical surgery for breast cancer two problems arise The first is at what stage in

TABLE 44

100 Cases of Primary Operable Breast Cancer

Overall	41% axilla +
	17% internal mammary +
	3% supraclavicular +
When axilla +	7% supraclavicular nodes +
	32% internal mammary nodes +
When axilla −	0 supraclavicular nodes +
	8% internal mammary nodes +

Dahl Iverson and Sorensen 1954

Findings in a series of 100 primary operable breast cancers undergoing radical mastectomy together with supraclavicular and internal mammary lymph node resections

the extension of radical mastectomy does the possible added salvage obtained by more extensive resection of lymphatic bearing tissues become negated by increased operative mortality morbidity and postoperative discomfort and disability? The second is at what stage in the progression of regional lymph node metastases does the disease become generalized and beyond the scope of surgical removal? The first and most logical step to be considered in the extension of radical mastectomy is the inclusion of en bloc resection of the internal mammary lymph node chain in continuity with the radical mastectomy procedure That this can be done without undue mortality and morbidity is shown by the 100 consecutive cases of primary operable breast cancer treated by this method at the Memorial Center with but one postoperative death and with an average hospital stay of eight days Furthermore we do believe that the internal mammary nodes can be involved in the absence of generalized systemic spread (in 10 of our cases the internal mammary nodes were involved while the axillary nodes were clear) and that the en bloc resection of

this lymph node depot will add to our salvage rate Radical mastectomy with en bloc in continuity resection of the internal mammary chain constitutes a rational theoretically effective surgical attack on the primary breast cancer together with *both* of its main primary depots of lymphatic drainage

Operative Technique

Radical Mastectomy with En Bloc in Continuity Resection of the Internal Mammary Nodes

In performing this procedure we have maintained the salient features of the classical radical mastectomy (en bloc resection, wide skin excision, meticulous thorough dissection of the axilla and thin skin flaps) and to this have added the en bloc in continuity resection of the internal mammary chain of lymph nodes By utilizing techniques which were previously described we have reconstructed the operative defect in the chest wall with a tense fascia lata graft covered by a sliding flap of skin and subcutaneous tissue from the opposite side

The entire anterior chest wall from one posterior axillary line to the other and from the base of the neck to the umbilicus is prepared for surgery Under gas-oxygen-ether endotracheal anesthesia an incision is made encompassing the tumor widely, extending from the pectoral-deltoid groove to the costal margin The incision is made at least two inches from the nearest palpable border of the tumor and in some instances lies over the center of the sternum, particularly when the lesion presents in the medial portion of the breast The incision is planned so as to

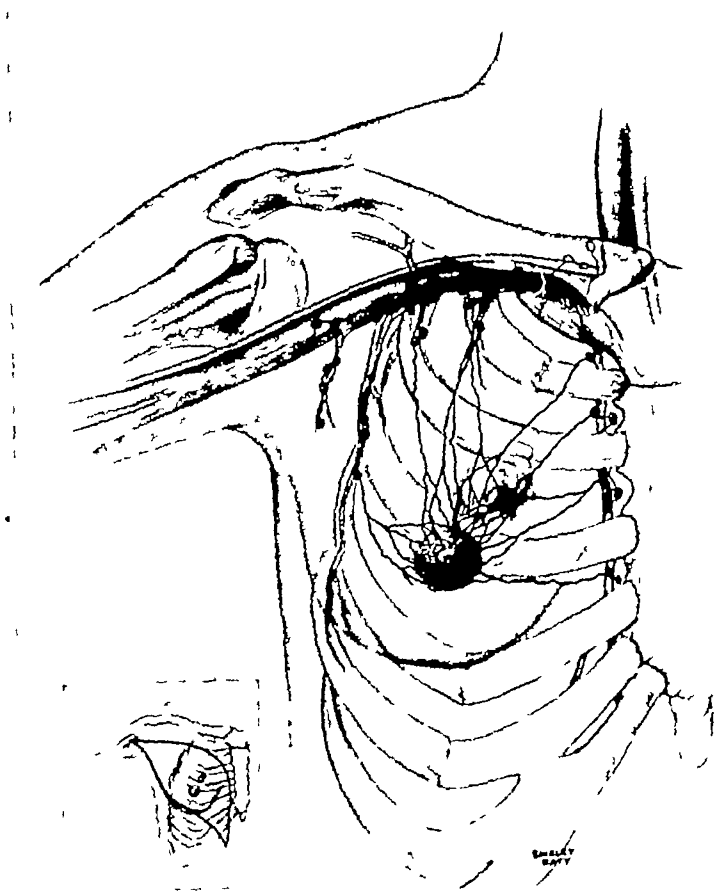


Fig 106 Diagrammatic sketch depicting the primary lymphatic drainage of the breast Inset The extent and type of incision used for upper inner quadrant lesions

include both primary tumor and nipple close to its center

An adequate amount of skin is included in the incision Thin skin flaps are developed to the opposite side of the sternum medially just beyond the edge of the latissimus-dorsi muscle laterally to the deltoid muscle and clavicle superiorly and to the costal margin below The overlying areolar tissue and the pectoral sheath is dissected from the clavicular portion of the pectoralis major muscle downward together with the operative specimen until the septum between the clavicular and sternal portions of the pectoral major muscle is met In a similar manner the anterior surface of the sternum is cleared reflecting the areolar tissue toward the operative specimen The lower chest wall is also cleared of areolar tissue up to the level of the fifth interspace If the lesion lies in the inferior inner quadrant of the breast the anterior rectus sheath is included in this portion of the dissection Laterally the latissimus dorsi muscle is cleared of areolar tissue, and its anterior border is exposed

Preparations are now made for dissecting the portion of the chest wall containing the internal mammary chain while still maintaining continuity between it and the overlying pectoralis muscle and breast The pectoralis major muscle is divided in its medial five cm between the sternal and clavicular bundles and the first rib is exposed Dissection is carried down to the first rib and to the arch of the manubrium these are cleared down to the upper border of the first interspace the pectoralis major muscle being reflected downward The first interspace is thus exposed in its medial four cm with the perforating vessels extending from the breast

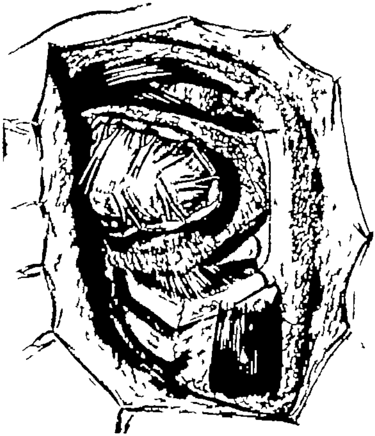


FIG 107 Second step Thin flaps have been developed the anterior surface of the sternum, the rectus muscle and the lower chest wall to the level of the fifth interspace have been cleared The pectoralis major muscle has been cleared over the clavicular portion and split between the clavicular and sternal portions to expose the first rib and the upper portion of the first interspace in the medial area. The dotted line depicts the incision made through the entire thickness of the chest wall including parietal pleura

into the internal mammary vessels through the first interspace still intact In a similar manner the sixth rib is cleared from below up to the lower border of the fifth intercostal space, here also preserving the continuity of the perforating vessels in this interspace In this manner the lower border of the first rib, the upper border of the sixth rib, the anterior surface of the sternum have been cleared without interfering with the continuity of the perforating vessels running between the internal mammary vessels and the breast between the first and sixth ribs During this stage of the operation the axilla is not entered so as to avoid any possible contamination of cancer cells from the axilla into the pleural space Rather the chest wall resection is completed and the chest wall defect closed before beginning the axillary dissection

The chest is now opened by inserting a straight clamp through the center of the first interspace about four cm lateral to the border of the sternum This opening is extended vertically The intercostal vessels are ligated and transected beneath the lower border of the first rib An exploring finger can now be inserted through this opening and the internal mammary artery palpated against the overlying first rib Likewise at this stage of the operation the base of the neck can be palpated from within the chest to determine whether or not gross metastatic nodes are present in this area, a finding which would negate this particular surgical attack With full control, since the chest is open and digital pressure may be applied against the first rib from within, dissection is carried along the lower border of the first rib and the internal mammary vessels are freed,

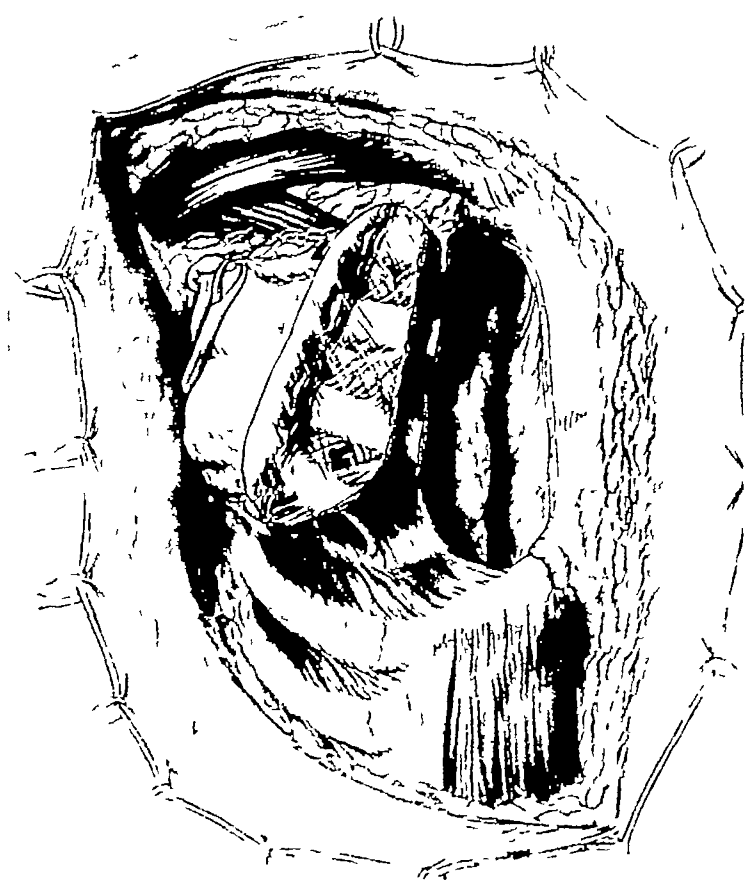


Fig 108 Third step The internal mammary vessels have been ligated and transected behind the first and sixth ribs The chest cavity has been entered through the upper end of the first interspace and the lower end of the fifth interspace The sternum has been cut one cm from its sternal border with a sternal splitting chisel Finally the ribs and intercostal soft parts intervening between the first and sixth ribs have been cut just lateral to the costochondral junctions with a heavy straight scissors and the resulting portion of the chest wall reflected lateralward, still in contact with the overlying pectoralis major muscle and breast

ligated with 00 black silk just behind the lower edge of the first rib and contiguous arch of the manubrium and transected In a similar manner the internal mammary vessels are ligated and transected just behind the upper border of the sixth rib At this stage the chest has been entered through the parietal pleura just behind and parallel to the lower border of the first rib and the upper border of the sixth rib Both these intercostal incisions are now joined by a sternal splitting incision The Lebsche sternal chisel is directed through the sternum about one cm from its ipsilateral border thus forming a trap door in the chest wall With blunt finger dissection the pectoralis major muscle is now lifted from the underlying chest wall lateral to its insertion This separation usually takes place just lateral to the costochondral junctions without any bleeding and without interfering with the normal attachment of the muscle which is located over the parasternal portion of the chest wall and usually extends for the width of the costal cartilages That portion of the chest wall which contains the internal mammary nodes and is still in contact with the overlying pectoralis muscle and breast is now separated from the chest wall by cutting through the ribs and intercostal soft parts just lateral to the costochondral junctions of the second third fourth and fifth ribs with a heavy straight scissors. This free portion of the chest wall containing the internal mammary chain is now reflected laterally still in continuity with the overlying muscle and breast Before any further dissection the chest wall defect is now repaired with a fascia lata graft sutured into the defect under tension This graft is obtained at the time of surgery by an assistant who uses a separate instrument tray and changes his gloves and gown in order to avoid any possible contamination from the operative area to the donor site The donor site is dressed with a snug pressure dressing and drained with two soft Penrose drains

A no 24 French whistle tipped right angle suprapubic type catheter is now inserted through the sixth or seventh interspace laterally with the intrathoracic portion of the tube lying parallel to the ribs and held in place by the right angle bend at its exit from the chest wall This is now attached to an underwater drainage bottle A layer of interrupted mattress sutures of no one chromic catgut is placed so as to approximate the fascia lata graft to the under surface of the bony chest wall defect thus creating a smooth surface where the graft opposes the lung These sutures are placed through the graft about one cm from its edge and then through the bony borders of the chest wall defect from within outward and are tied over the bony margins of the chest wall defect Maximum stretch is applied to the graft This is accomplished by placing the lateral mattress sutures through the fascia lata graft where the graft just meets the cut margins of the ribs under normal tension The mattress sutures are then passed through the intercostal soft parts about three mm. from the edges of the ribs and about two cm beyond the cut edge of the ribs 'cheating' in order to obtain tension of the fascia lata graft when the sutures are tied about the ribs Maximum stretch is obtained by placing all the sutures initially then over correcting the closure of the chest wall by depressing the ribs toward the sternum, holding them in this position while all the sutures are tied very snugly about the ribs. Maximum tension is obtained through the elasticity of the rib cage which springs back laterally when the pressure applied to it is relieved Adequate support and good closure is usually obtained The free borders of the graft are now sutured down about the operative defect with interrupted 000 black silk or fine catgut sutures.

FIG 109 Fourth step Illustrating the fixation of the fascia lata graft to the under surface of the borders of the chest wall defect with mattress sutures of no 1 chromic catgut A no 24 right-angled whistle-tipped catheter has been inserted into the chest cavity through the sixth interspace and attached to an underwater drainage bottle

With the chest cavity closed and with the underwater drain functioning the operation is now concluded as in a classical radical mastectomy The pectoralis major muscle is severed from its tendinous attachment to the humerus The pectoralis minor is freed from its insertion on the coracoid and the exposed axilla is now carefully and meticulously dissected clear from above downward and lateralward The pectoralis minor muscle is separated from the chest wall, and the dissection is completed just inside the latissimus dorsi muscle after dissecting off the anterior serratus muscle sheath The thoracodorsal nerve and vessels are routinely sacrificed If the axilla appears clear, the long thoracic nerve is cleared carefully and preserved, otherwise it is included in the dissection The operative specimen is removed, and the wound is closed

In order to facilitate closure and to strengthen the support of the chest wall defect, the opposite breast is mobilized from the underlying pectoral sheath for a distance of about six to ten cm from the sternal border It is then split from underneath for a depth of one or one and a half cm and the resultant mobilized flap is slid across and sutured to the borders of the chest wall defect with interrupted stay sutures of no 1 chromic catgut in order to bolster the fascia closure of this defect Surprisingly little deformity is caused by this maneuver

The underwater catheter is now put through a stab wound in the lateral skin flap which is tacked down to the chest wall with through-and-through stay sutures tied over gauze bolsters The skin incision is now closed with interrupted 000 black silk sutures Tension in the skin incision is avoided

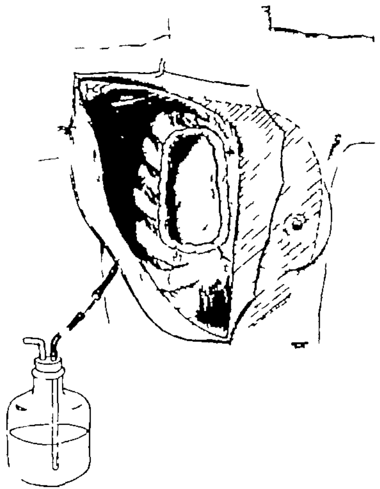


FIG 110 Fifth step The closure of the chest wall has been completed with the fascia lata graft under tension Radical mastectomy has been concluded in the usual manner The opposite breast has been undermined to the extent of the crosshatched area in order to form a sliding flap pedicle to reinforce the closure of the defect in the chest wall

by the use of stay sutures in both flaps Two Penrose drains are inserted one in the lower angle extending beneath the opposite breast and the other draining the axillary region A snug dressing of gauze fluffs and Dakin pads is applied over the chest wall with tense elastic adhesive dressings applied over a six inch gauze bandage

An expert anesthetist well trained in endotracheal anesthetic technique is essential for the successful performance of this procedure At frequent intervals during the procedure positive pressure is exerted in order to expand the lung and by so doing prevent atelectasis Tracheal aspiration is also performed for the same reason During the procedure intravenous fluids are administered the average patient requiring about 1 500 cc of blood 250 cc of saline and about 1 000 cc of glucose and distilled water Another 1 500 cc of distilled water with five per cent glucose and vitamins is administered later in the day

Postoperative Care

1 On returning to her room the patient is checked by a bedside (portable) postero-anterior roentgenogram while she is being supported in an upright position in order to rule out pulmonary atelectasis effusion or pneumothorax.

2 Special nursing care is provided for the first 48 hours postoperatively

3 Nasal oxygen is administered by nasal catheter if needed This is usually not necessary

4 Tracheal aspirations are performed

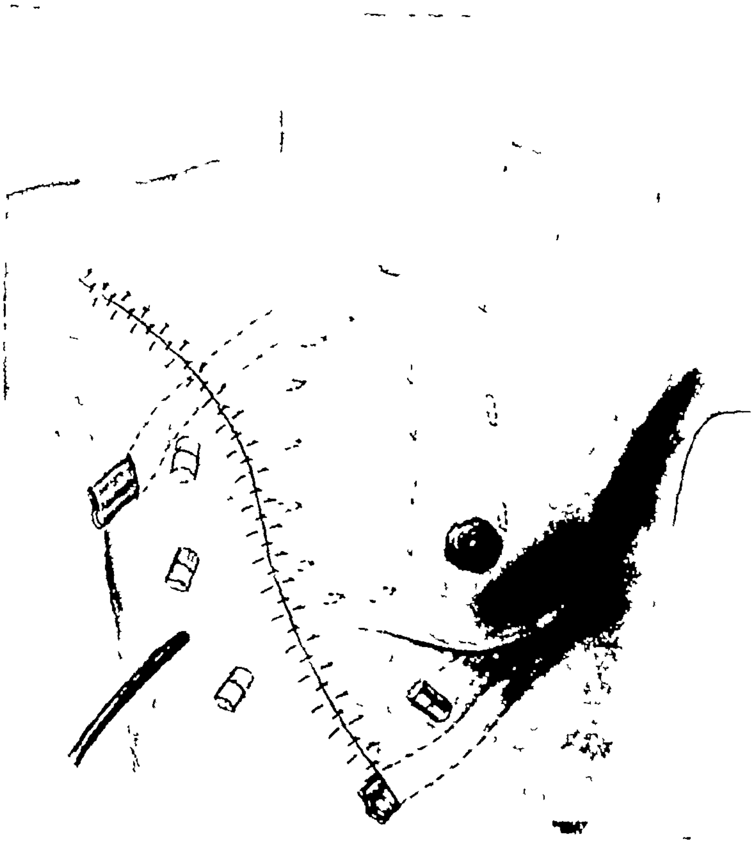


FIG 111 Final step in the operative procedure The opposite breast has been slid across the midline partially and tacked down to the chest wall with buried stay sutures of no 1 chromic catgut The lateral flap is sutured to the chest wall with several through-and-through mattress sutures tied over gauze bolsters Soft Penrose drains are inserted in the axilla and beneath the opposite breast Primary closure is usually obtained

twice daily for the first three postoperative days

5 Penicillin aerosol inhalations are administered three times daily for the first four postoperative days

6. The patient is encouraged to breathe deeply and to expectorate any accumulation of mucus which forms in the tracheo-bronchial tree

7 300,000 units of procaine penicillin are given intramuscularly twice daily for one week postoperatively

8 Blow bottles are used four or five times daily

9. A steam kettle is kept at the bedside in order to moisten the air, particularly during the cold dry months, in order to relieve tracheitis resulting from the insertion of the endotracheal tube

10 Narcotics are given when necessary for pain (Pantopon® gr ⅓ q 4 hrs prn or Demerol® 75 mgm q 4 hrs prn)

11 A regular diet is ordered when the patient can tolerate it, usually within the first 24 hours after surgery Supplementary intravenous fluids are usually necessary during the first postoperative day

12 The underwater drain tube is removed in 48 hours postoperatively The tube is removed without disturbing the main portion of the dressing and as it is being removed a plug of vaseline gauze is applied over the opening of the chest wall to seal it off

13 The patient is redressed on the fifth and seventh days postoperatively and is usually discharged from the hospital on the seventh or eighth postoperative day

We have had only one postoperative death out of 160 patients operated on until the present time This occurred in a 62-year-old female with hypertension who died of a cerebral vascular thrombosis two days postoperatively, following an apparently uneventful initial recovery

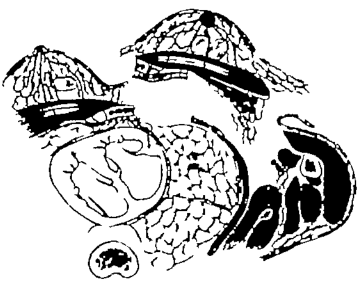


FIG 112 A diagrammatic sketch of the operative specimen showing the relations between the primary tumor lymphatic draining vessels and the primary lymph node depots draining the breast (Suggested by R S Handley)

FIG 113 Internal aspect of the operative specimen following clearing of the internal mammary nodes in pathology laboratory Portions of the sternum and the second third fourth and fifth rib are still attached to the overlying pectoralis major muscle

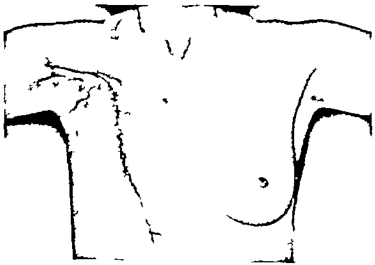


FIG 114 Postoperative appearance of the patient This patient was operated upon three years ago and showed an infiltrating duct carcinoma grade III one and a half cm in diameter beneath the right areolar margin One node metastasis six mm in diameter was noted in the third intercostal space of the internal mammary chain She is free of disease at present and has perfect function no paradoxical motion of the chest wall and is back to her normal range of activities

FIG 115 Patient demonstrating a postoperative complication which has occurred three times in our series Skin flaps have separated exposing a large portion of the fascia lata graft which is holding well and has become covered with granulation tissue

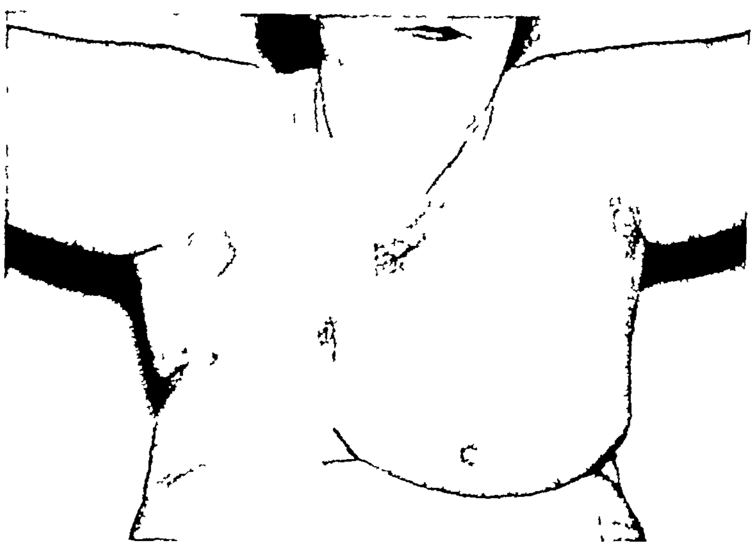


FIG 116 Same patient three weeks following secondary closure by re-approximation of the mobilized flaps Good function and minimal paradoxical motion were obtained We believe the fascia lata graft may very well have avoided a postoperative mortality, and certainly in this instance has avoided empyema

We insist upon the use of a tense fascia lata graft in closing the defect in the chest wall In addition to affording firm support and diminishing paradoxical motion in this area, the graft has acted as a life-saving closure of the chest wall in several patients in whom the overlying skin flaps sloughed either from necrosis or infection In no case have we had any evidence of fascia lata slough

Operative Findings

At present 160 patients have undergone this operative procedure These patients ranged in age from 30 to 70 years No appreciable increase in morbidity and only one postoperative death has occurred in this group of 160 cases This is less than one per cent operative mortality

At present, in the first 150 cases operated upon, positive internal mammary nodes were found in 36 per cent while the axillary nodes were positive in 54 per cent Thirteen per cent of those patients in whom the axillary nodes were negative had positive internal mammary nodes Six per cent of the entire group operated upon had only internal mammary nodes involved One quarter of the patients operated upon had primary lesions presenting in the outer half of the breast while three quarters of the patients had medial lesions This preponderance of

inner half lesions in this series was specially selected because of the greater likelihood of internal mammary node metastases with the inner quadrant tumors We have only one case in the outer quadrant in which the axilla was negative while involvement was noted in the internal mammary nodes However when the axillary nodes were positive, 60 per cent of the medial lesions showed positive internal mammary nodes, and 44 per cent of the outer quadrant lesions also showed positive internal mammary nodes

In two patients no gross nodes were found in the internal mammary chain The number of nodes varied in the individual cases from none to 12 The greatest frequency of nodes was noted in the first second and third interspaces. In 45 cases with positive internal mammary nodes the highest incidence was noted in the following order second interspace third interspace first interspace fourth and then finally only two cases with positive nodes in the fifth interspace In the first 50 cases with positive internal mammary nodes there was a great preponderance of positive nodes to the medial side of the internal mammary vessels. The medial nodes were positive in 82 per cent of all cases while the lateral nodes were positive in only 54 per cent of all cases In almost one half of the cases only the medial nodes were involved

Adequate follow up is impossible at present since the earliest operation was performed only 3½ years ago However at present we do have several patients who were operated upon between two and three years ago who had positive internal mammary nodes and who are free of disease at present In only one instance did a patient in this group of 160 cases develop a local recurrence prior to the development of widespread systemic disease In this particular patient disease was very extensive at time of surgery and nodes were involved at all levels in the axillary and internal mammary nodes

TABLE 45

45 Cases with Positive Internal Mammary Nodes

Interspace	Number Involved	Involvement
1	19	5 had only 1st interspace involved 8 had extensive node involvement
2 3	31 24	23 had only 2nd or 3rd or both involved
4	10	7 had widespread involvement
5	2	Both had extensive node involvement Both dead

Showing the relative involvement of the various parasternal interspaces in the first 45 cases with positive nodes

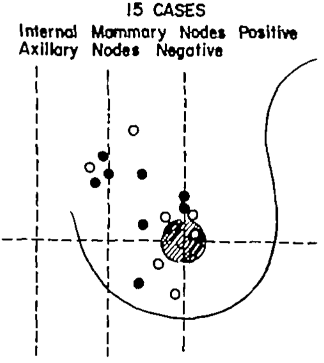
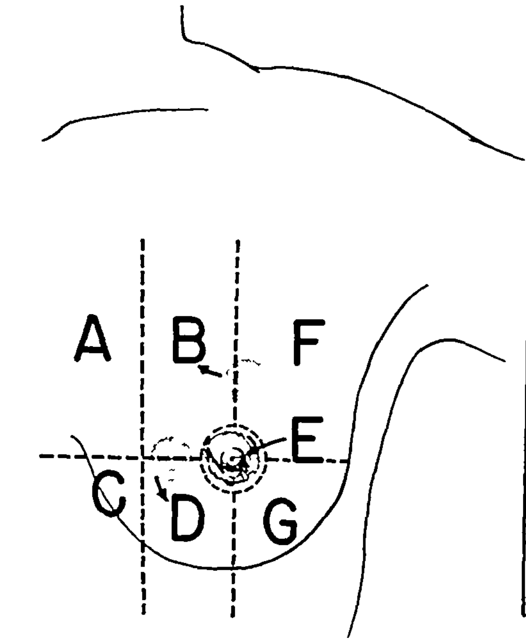


FIG 117 Diagram showing the location of primary lesions in cases when the internal mammary nodes were positive in the absence of axillary node involvement Open circles represent cases of Dr Everett Sugarbaker solid circles comprise our own group



Location	A	B	C	D	E	F	G	TOTAL	
Total number of cases	23	60	17	17	15	14	4	150	100 %
All nodes clear	9	27	8	8	3	3	1	59	40 %
Internal mammary only invaded	3	4	0	1	0	1	0	9	6 %
Axillary only invaded	1	15	4	3	5	6	3	37	24 %
Both internal mammary and axillary invaded	10	14	5	5	7	3	1	45	30 %
Overall Group	150 Cases	40 % All nodes clear 36. % Positive internal mammary 54 % Positive axillary 6 % Only positive internal mammary 13 % Cases with clear axilla had positive internal mammary							

TABLE 46

Node Metastases in Primary Operable Breast Cancers Undergoing Combined Procedure

Lesions touching the vertical lines are assigned to the sector lying on the sternal side of that line, those touching the horizontal lines are assigned to the lower sector Lesions lying behind the areolar and nipple are assigned to sector E

Operative findings in the first 150 cases undergoing radical mastectomy with in continuity en bloc excision of the internal mammary chain

TABLE 47

Node Findings in 150 Cases

	Lateral	Medial	Total
	%	%	%
Number	37–25	113–75	150–100
All nodes clear	9–25	50–44	59–40
Int mammary nodes +	1–3	8–7	9–6
Axillary nodes +	15–40	22–20	37–24
Both int mammary and axillary nodes +	12–32	33–29	45–30

If axillary nodes are +, then int mammary nodes are + in
55% Overall group
60% Medial half
44% Lateral half

If axillary nodes are −, then int mammary nodes are + in
13% Overall group
14% Medial half

Findings in the first 150 cases undergoing the combined procedure Breast divided by a line going vertically through the center of the nipple Cases are assigned to the side in which the major portion of the tumor presented

Evidence of the practicability of this operative procedure is the fact that the average hospital stay following this procedure was seven to eight days In no instance has any appreciable interference with the patient's normal activities ensued All patients operated upon have returned to their former state of activity

Summary and Conclusions

A short resumé of the present trends in extended radical surgical attack on breast cancer has been presented together with a more detailed description of our own experience with radical mastectomy combined with en bloc resection of the internal mammary lymph node chain It is still too early to evaluate the results of these more radical surgical procedures And, since so many variable factors are involved, the final evaluation will be a complicated and difficult one

At present the best five-year survival rates in any series of significant size have been obtained through the classical surgical pro-

cedure of radical mastectomy In the larger hospitals these results have excelled those obtained through a combination of conservative surgery plus intensive radiotherapy

In order to increase the salvage rate of primary operable breast cancer through extended radical surgical treatment, several conditions must prevail

1 The salient features of the classical radical mastectomy must be preserved—wide skin excision meticulous and thorough dissection of the axilla, thin skin flaps, en bloc resection—and to this must be added the en bloc resection of other primary lymphatic drainage depots and in some instances possibly secondary drainage areas as well

2 The more extensive procedure should be well planned so as to avoid undue morbidity and postoperative mortality

3 The more extensive operation should be applied only to patients whose general physical condition will tolerate this procedure and in whom one has reason to believe that the disease has not progressed beyond the regional lymphatics. More radical surgery goes hand in hand with early diagnosis and early therapy

4 The more radical surgery is necessarily somewhat more difficult and should be undertaken only by competent surgeons, with the assistance of an excellent anesthesist and with sufficient attention to postoperative care Otherwise postoperative mortality and morbidity will become prohibitive

The two main problems to consider in extending radical surgical treatment for breast cancer are

1 At what stage in the extension of radical mastectomy does the possible added salvage obtained by this more extensive resection of lymphatic bearing tissues become negated by increased operative mortality morbidity and postoperative discomfort and disability?

2 At what stage in the progression of regional lymph node metastases does the disease become generalized and beyond the scope of surgical extirpation? The most logical step to be entertained in considering extension of radical mastectomy is the addition of in continuity en bloc resection of the internal mammary lymph node chain which is a primary lymphatic drainage depot of the breast In our own hands this has proven a feasible operation with minimal postoperative complications and with less than a one per cent postoperative mortality Thirty-six per cent of the patients undergoing this procedure showed metastatic nodes in the internal mammary chain When the axillary nodes were negative 13 per cent showed internal mammary node metastases

Further extension to include a supraclavicular node dissection has already been done In most instances this has not been an in continuity procedure In one case we have performed an en bloc in continuity resection of the breast axillary internal mammary and supraclavicular regions in a patient with a local recurrence of the chest wall Although this procedure did not result in any particular dysfunction or deformity we have not been very optimistic concerning the possibility of increasing the salvage rate with this particular type of surgical extension It is likely that the majority of patients with metastatic cervical nodes from breast cancer already have subclinical systemic metastases since the lymphatic vessels draining the breast empty into the junction of the jugular and subclavian veins Nevertheless it is possible that some patients may be salvaged through this extensive procedure

It will be most interesting to observe the final results of these various procedures Rationally we may expect to salvage a greater proportion of primary operable breast cancers through a combination of early diagnosis and well planned more radical surgical treatment Only time will tell!

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CHAPTER XIII

Postoperative Care

Modern surgery embraces not only surgical diagnosis and operative treatment but also preoperative preparation postoperative care and in the case of breast cancer, ultimate rehabilitation and further follow-up Based upon sound physiologic principles every effort is made to aid the body in its efforts to recuperate—to reduce, as Moore (19) has so aptly said 'the burden on the patient s biologic response " With the continued improvement of anesthesia and a more general acceptance of the concept of total surgical care uncomplicated recovery will become more and more frequent even following such major surgical procedures as radical cancer surgery

Return from the Operating Room

Upon leaving the operating room the patient is usually sent to the recovery room where consciousness is quite quickly regained because the plane of anesthesia has been light This represents an ideal situation, as noted by Elman (10) in that it reduces the depressant and toxic effects of prolonged anesthesia and avoids accidents which are more likely to occur to the unconscious patient

During transportation from the operating room every effort should be made to avoid injury to the flail arm on the side of operation The arm is placed on a pillow alongside the body where it is carefully protected from falling over the side of the litter or bed or from over-extension during turning

The patient is turned frequently during the first 24 hours during which time the arm is supported on a pillow If drainage is profuse, supplementary protective gauze pads may be placed over the drainage area but it is seldom necessary to release the pressure or redress the wound completely before the third or fourth postoperative day Negative pressure drainage avoids the necessity for early redressing

A normal diet after radical mastectomy should be resumed as rapidly as possible Some younger patients may experience little or no digestive difficulty and under these favorable circumstances a full diet may be started within the first 48 hours

Ambulation

Unless there is some specific contraindication early ambulation is started as soon as possible by allowing the patient to sit on the edge of the bed with her feet resting on a chair This may be done during the first 24 hours During the first or second postoperative day the arm should be supported by a sling or allowed to rest on a pillow while the patient is sitting or standing up Graded resumption of normal ambulatory mobility is begun as soon after the first postoperative day as possible Movement of the legs is encouraged while the patient is in bed, and breathing exercises are important as an aid to full respiratory function

Prophylactic Chemotherapy

The use of antibiotic therapy following dical breast surgery as a prophylactic ocedure is a matter of individual convicon I find it to be of definite value and nsider it desirable The justification for e prophylactic use of antibiotic therapy s in its ability to control wound infection hereby decreasing the role of this factor lymphedema) and diminish the incidence pulmonary complications due to infection satisfactory routine is to give the patient 0,000 or 600,000 units of aqueous penicillin renterally twice daily Broad spectrum tibiotics given orally can also be used ite effectively This should be discontinued soon as the surgeon is confident that the nger of infection is over or shortly after e removal of the drain Delayed wound ection by organisms held in abeyance ile the patient is under the influence of tibiotic therapy is always a real possibility d may occur as a late complication

Pulmonary Complications

Postoperative pulmonary complications ntribute to both the morbidity and mority of radical mastectomy Such condins as penumonia, aspiration pneumonia, lmonary atelectasis, pleurisy, pulmonary ema and pulmonary embolism are more less serious complications which may be ated to the prolonged anesthesia and the tensive radical operative procedure

The physiology of the lung makes it parularly prone to disturbances which intere with its dynamics and normal function poventilation is the one most important tor responsible for disturbed function is may occur as a result of the operative uma of radical breast surgery or limitan of respiration due to postoperative pain allow breathing produces an uneven ventiion of the lungs and clinically demonsble anoxemia

Extensive chest wall surgery and the use of a tight, constrictive binder interfere with the patient's ability to aerate the lungs properly or to evacuate the tracheobronchial tree of secretions Adequate pulmonary ventilation will minimize many of these respiratory complications Deep-breathing exercises, relief of postoperative pain, early ambulation and the use of adhesive elastic pressure dressings in place of tight, inelastic constrictive binders coiled around the body are all important factors in improving pulmonary ventilation following radical mastectomy

Thromboembolic disease occurring as a postoperative complication is always a potential major problem and serious threat to life The avoidance of trauma to the lower extremities, the promotion of venous flow by exercises, change in position and early ambulation are excellent prophylactic procedures There are several clinical investigative studies which indicate a close relationship between neoplastic disease and an increased incidence of thromboembolic complications The cause of this venous thrombosis is unknown but it is thought to be related to tumor necrosis and host response

Care of the Wound

The first complete change of dressings should be made on about the fourth postoperative day unless there is some indication to inspect the wound at an earlier time At the initial redressing the drain may be removed or shortened, depending upon the local conditions of the wound The negative pressure drain should be removed at this time In reapplying the dressing, it should again consist of an adhesive elastic pressure bandage similar to the original dressing

On the sixth postoperative day the wound is again inspected and the dressings changed The alternate skin sutures are removed and the pressure dressing reapplied

All of the remaining sutures are removed

by the eighth or ninth postoperative day and the patient is permitted to be freely ambulatory about the hospital Use of the arm is encouraged for feeding dressing washing and in particular combing the hair (see page 323)

If postoperative radiotherapy is to be administered it may be expedient to start this while the patient is still in the hospital It is desirable to begin radiotherapy early on about the fourteenth postoperative day If postoperative radiotherapy is not indicated then the patient may be discharged from the hospital on about the tenth to the fourteenth day depending upon the local condition of the wound It has been our practice to administer postoperative radiotherapy (see Chapter XV) to all patients who have evidence of axillary metastases by microscopic examination Although it is advisable to start this therapy as soon as possible, it may be more practical and less expensive to have the patient return for radiotherapy on an ambulatory or out-patient basis shortly after leaving the hospital

Delay in wound healing is usually the result of flap necrosis This may be shown by a mere superficial skin slough of a small avascular area in the lateral flap incisional margin or may involve a greater or lesser amount of full thickness of skin necrosis adjacent to the incision or elsewhere. This is by far the most common postoperative complication of radical mastectomy and may result in a prolonged hospital stay, a possible secondary skin grafting procedure or a temporary delay in the initiation of radiotherapy

The cause of this complication is almost always the impairment of blood supply along the medial margin of the long lateral flap Undue tension on a long and poorly nourished skin flap which perhaps has been dissected a little too thin is the *principal reason* for flap necrosis Tight dressings and a serous accumulation of fluid under tension contribute to this complication

The problem of wound infection has been dealt with previously in the section on drainage and the consideration of antibiotic therapy

Lymphedema of the Arm Following Radical Mastectomy

Surgeons radiotherapists and general practitioners alike are all seriously concerned with the unfortunate complication of lymphedema of the arm following radical mastectomy In the opinion of some physicians this shortcoming of radical surgery repudiates the value of the entire Halsted operation. The partisans of this shortsighted perspective however, are more concerned with morbidity than with mortality

Unfortunate as this complication may be when caused by recurrent malignant disease, it is indeed a distressing occurrence when it follows an otherwise successful surgical operation Not infrequently patients themselves become more disturbed about the appearance of their swollen arm than about the amputation and loss of their cancer bearing breast In each community there are always a few conspicuous cases in whom lymphedema and partial disability perpetuate a public fear and apprehension of this postmastectomy complication Among some of these patients the gossip of their postmastectomy problems loses nothing in the telling There is even a suspicion abroad that in some unenlightened areas surgeons themselves are so anxious to preserve their reputation from the liability of this conspicuous complication that radical mastectomy is frequently foregone in favor of simpler surgery

Incidence

Lymphedema of the homolateral arm following radical mastectomy for breast

cancer, in the absence of metastatic or recurrent disease in the regional nodes, occurs in a large number of patients. This swelling is usually asymptomatic or slight and may be entirely overlooked on casual inspection unless actual measurements are made. However, occasionally the swelling can be severe, extremely painful and most disabling.

In a very careful consideration of postmastectomy swelling, Lobb and Harkins (18) noted some enlargment of the arm present in 80 per cent of their 51 patients. Thirty-one per cent of these patients had only slight swelling (less than 1.5 cm.), 27 per cent had only moderate swelling (1.6 to 2.9 cm.), and 22 per cent had marked swelling (3.0 cm. or more). The effect of right-handed or left-handedness was critically considered and found to have no bearing on the problem. A few patients with simple mastectomy were studied and 50 per cent of these were also found to have some degree of postoperative lymphedema. There was a suggestion that the decreased tissue turgor of older patients may have increased the tendency toward arm swelling. However, Conway and Neuman (5), on the contrary, found arm function to be less impaired among the older patients.

At the turn of the century, Handley (15) noted that "the brawny arm occurs in about one case out of every six of breast." Halsted (14) commented that "edema following operative blocking of the lymphatics is most frequently observed after the radical operation for cancer of the breast. For many years I was unable to account for the fact that in some instances a year or two or more after this operation and without return of the disease there would occur, suddenly or perhaps slowly, a swelling, occasionally very great, of the upper extremity."

Holman, McSwain and Beal (16) examined 100 patients who had been subjected to radical mastectomy, the period of time postoperatively ranging from six months to 11 years. An analysis of these cases indicated that some degree of lymphedema of the arm was present in 70 per cent of their patients. Twenty-six per cent had swelling of 3 cm. or less, 33 per cent had swelling of 3 to 6 cm., and only 11 per cent had very marked swelling of more than 6 cm. These authors call attention to the latency of this condition by noting that "a significant degree of swelling may exist without recognition unless measurements are made." The percentage of patients with lymphedema appeared to be slightly lower when a skin-graft closure was performed.

The studies of Deaton and Bradshaw (7) revealed some degree of lymphedema in about 50 per cent of their patients. However, only nine per cent had marked postmastectomy swelling. There appeared to be little relationship between lymphedema and functional use of the arm. Nicholson and Grady (20) examined 230 cases after radical mastectomy and reported arm swelling in 44 per cent.

Daland (6) found no swelling in the circumference measurement of the upper arm in 45 per cent of 90 patients after radical mastectomy, slight swelling (1 to 2 cm.) occurred in 31 per cent, moderate swelling (2.5 to 4.5 cm.) in 17 per cent, and severe swelling in 5.5 per cent.

Guthrie and Gagnan (13) examined 100 patients following radical mastectomy and found only eight with postoperative lymphedema. In six of these eight patients the swelling was said to have subsided with conservative care.

Thus, it is readily apparent that despite the virtues of radical mastectomy, this procedure carries with it quite frequently the risk of postoperative lymphedema of the arm. Although usually slight and but a minor impairment, this postoperative sequela may or may not be severe, progressive, disabling

and/or intensely painful However criticism of this complication comes easier than its surgical avoidance It usually appears early in the postoperative period but may develop suddenly or slowly after several years.

Stewart and Treves (24) have recently defined a heretofore unrecognized clinical entity of lymphagiosarcoma which occurs rarely and only after a long latent period in patients with postmastectomy swelling of the arm These authors reported six cases of postmastectomy swelling which occurred without axillary metastases, with and without postoperative radiotherapy and were characterized by the development of extensive sarcomatous tumors in the lymph edematous arm

Etiology

Lymphedema as the word is commonly used refers to a swelling of the subcutaneous tissues due to the presence of excessive lymph fluid The accumulation of postmastectomy lymphedema usually occurs as a result of an excisional defect in the regional lymphatics of the upper extremity By definition this excludes edema of cardiac renal or nutritional origin The presence or absence of lymphedema depends upon the rate of lymph formation compared with the rate of lymph removal Chronic lymphedema of the arm results in an increased thickening in the skin and subcutaneous tissues in addition to an hypertrophy of the fibrous connective tissue stroma

Regional edema of the upper extremity also may occur as the result of disease or obstruction of the axillary or subclavian veins. While the mechanism of this type of edema remains to be clarified it is generally considered to be due to 1) increased venous pressure as the result of partial or complete venous obstruction and 2) a decreased rate of venous blood flow as the result of obstruction or vascular incompetence During the complete axillary dissection and subsequent treatment a combination of factors may exist to readily cause postmastectomy swelling of the arm

In the classic paper entitled "The Swelling of the Arm After Operations for Cancer of the Breast—Elephantiasis Chirurgica—Its Cause and Prevention" Halsted (14) did much to stimulate interest concerning the basic problems of this postmastectomy complication 'For many years I entertained the view that, although blocking of the lymphatics and occasionally also of the veins was the underlying factor infection played a conspicuous part in the determination of the amount of the swelling and the time of its manifestation

Since this original contribution by Halsted, at least two schools of thought have appeared regarding the pathogenesis of this condition Devenish and Jessup (8) believed that the interruption of the axillary lymphatics played the predominant role in arm swelling They demonstrated that direct venous pressure studies showed only a minor variation between normal arms and the arms of postmastectomy patients Using dye injections they also demonstrated distinct variations in lymph drainage between normal and abnormal arms This work has been confirmed by several investigators

Sponsoring a contrary point of view Veal (27) has observed an increase in venous pressure and has confirmed the presence of venous obstruction by venography in patients with postmastectomy edema. "Edema resulting from obstruction of the axillary and subclavian veins is by far the most common cause of swelling of the arm following operation The most frequent cause of venous obstruction is recurrence of the malignancy along the course of the veins In some cases the venous occlusion results from benign scar formation Lymphatic stasis is a secondary result of venous obstruction which

if prolonged will lead to permanent blockage of the lymphatic flow. Infection is prone to develop and may lead to further obstruction and cause a greater degree of swelling."

Deaton and Bradshaw concluded from their clinical investigations that increased venous pressure, presumably due to blockage of the axillary vein, does not seem to be an important etiologic factor in postmastectomy edema. Infection with its excess scar tissue formation appeared to be the prime pathogenic factor.

Russo, Parker and Mathews (23) concluded that after radical mastectomy changes in the axillary vein could be readily demonstrated. These varied from a mild degree of distortion to a complete occlusion of the axillary vein. After a period of three or four months these alterations in the caliber of the axillary vein usually disappeared. These investigators recommend prophylactic bandaging of the arm as a worth while preventive measure to reduce the incidence of lymphedema following radical mastectomy.

The pros and cons of many other factors have been considered as contributory causes in the development of lymphedema of the arm. Conway and Neumann (5) found the incidence of postmastectomy lymphedema to be significantly increased in those patients who received postoperative radiotherapy. However, as far as could be determined by Holman, McSwain and Beal (16), radiotherapy "per se did not tend to cause swelling unless it was associated with dermatitis, when the swelling was apparently attributable to it."

Oberhelman (21), Adair (1), and Bell (2) all reported an increased incidence of lymphedema of the arm following radiotherapy and Oberhelman considered the cause to be excessive radiation fibrosis. Deaton and Bradshaw could find no relationship between postoperative edema and radiotherapy. Gratzek and Stenstrom (12) regarded the relationship between radiotherapy and lymphedema as controversial and again noted the variation in reported incidence and scarcity of reliable statistical data. Daland (6) concluded that X-ray therapy in addition to radical surgical dissection were both important causes of postoperative arm swelling. The avoidance of infection, early motion and a carefully placed incision which does not encroach upon the arm or axilla were also considered factors of importance in preventing postoperative lymphedema.

Conway and Neumann found full function of the arm in a larger percentage of patients when the wound was closed by skin-grafting. Swelling of the arm had a slight positive correlation with the following three factors in the series of patients studied by Lobb and Harkins: 1) radiotherapy, 2) skin recurrence, and 3) impaired arm function. However, in their series, lymphedema appeared to have no correlation with 1) wound infection, 2) skin-grafting and 3) axillary metastases. The importance of avoiding an axillary dead-space was emphasized by Trueblood (26). Arm exercises were favored and they were to be encouraged early. Holman, McSwain and Beal concluded that "skin grafting has no influence on the occurrence of swelling of the arm following radical mastectomy." The presence or absence of axillary metastases at the time of operation was found to have no bearing on lymphedema. The most important factors by far were considered to be infection and X-ray dermatitis.

Halsted advocated suturing the skin edge at the upper margin of the incision to the muscles of the first intercostal space, thereby raising the axillary fornix, eliminating the dead-space and preventing tension on the operative incision. His view regarding the role of infection as a leading cause of surgical elephantiasis (elephantiasis chirurgica) is best expressed by his own statement, "that the records support our view that infection

is very frequently, if not indeed usually the overlying cause of the swelling of arms whose main lymphatic channels have been more or less blocked by operation. The infection may quite conceivably be so mild in degree as to escape the observation even of those intently on the lookout for it"

Villasor and Lewison (28) have recently surveyed by individual examination two series of postmastectomy patients, with and without arm swelling in a comparative clinical consideration of lymphedema The following multiplicity of factors were specifically investigated in this study of postmastectomy patients

- Age
- Predominant hand
- Degree of lymphedema
- Function of arm
- Relation to surgery
- Relation to axillary metastases
- Disease or injury to axillary vein
- Excision of clavicular head of pectoralis major muscle
- Weight (obesity)
- Size and location of primary tumor
- Pain
- Onset of swelling
- Relation to radiotherapy
- Skin-graft or primary closure
- Position of scar
- Drains
- Aspirations
- Dressings of wound
- Position of arm
- Wound infection
- Mobilization of arm
- Regional recurrence of metastases
- Injections or trauma to arm
- Constitutional diseases
- Infections of hand or arm

The results of this study indicate that the precise cause of lymphedema remains very difficult to determine It could not be shown for instance that arm swelling was due to one or two predominant factors which were either obvious or undeniable *There was no determinant common denominator found which could be constantly held responsible for the development of this condition* In 57 per cent of the patients postmastectomy lymphedema developed shortly after operation without any one determinant causative factor Yet, among the multiplicity of factors which appeared to bear some relationship to the pathogenesis of this postoperative problem were 1) wound infection 2) axillary metastases 3) immobilization of the arm, 4) radiotherapy, and 5) injections into the affected arm Other factors possibly contributing to this complication appeared to be obesity injury or phlebitis of the axillary vein poor position of the scar and the removal of the clavicular head of the pectoralis major muscle

Treatment

Prevention

Once swelling of the arm occurs and persists, treatment by either conservative or surgical means is seldom satisfactory Although it has been said that it is easier to prevent postoperative edema following radical mastectomy than to cure it after it has occurred yet the prophylactic measures employed must in no way compromise the value of the radical operation

The following factors appear to be important coefficients in the prevention of postmastectomy lymphedema

1. Secure primary wound healing without skin slough or infection
2. Meticulous sharp axillary dissection is desirable to minimize local trauma and prevent local recurrence
3. Prevent fluid accumulation in the axillary dead-space
4. Early mobilization and graded exercises of the arm

FIG 118 Marked postoperative lymphedema of the arm in an obese patient with extensive local recurrence and infection The patient had had intensive radiotherapy This distressing condition was associated with pain, "heaviness" and disability

5 Carefully administered radiotherapy to avoid the hazard of serious radiodermatitis
6 The position of the incision should not cross or encroach upon the shoulder or axilla
7 Avoid damage to the axillary vein
8 The clavicular head of the pectoralis major muscle should remain intact as a support and protection for the neurovascular structures
9 Every care should be taken to avoid even minor infections of the homolateral hand or arm Erysipelas should receive prompt and intensive treatment
10. Injections of any kind are contraindicated in the homolateral arm

These precautions are advisable to aid in preventing the complication of swelling of the arm Yet despite these recommendations failures will occur, but their incidence will be lessened by strict adherence to these surgical principles which reflect the best we know

Conservative Measures

Conservative treatment, like surgical treatment, is seldom of striking or permanent benefit A palliative regime for the conservative management of patients with postmastectomy lymphedema has been described by Foley (11) The application of certain physiologic principles has resulted in the development of a program of treatment which employs elevation (gravity), an elastic sleeve or bandage (compression), physiotherapy (massage and effluvage), and a low salt and fluid intake (dehydration) "Marked improvement in swelling, pain and cosmetic appearance has resulted in a small group of patients so treated "

Diuretics have been useful in the treatment of generalized or cardiac edema and may have a beneficial role in the control of lymphedema of the arm The mercurial,

xanthine or newer acetazoleamide (Diamox®) diuretics all may be of value in this postmastectomy problem Minor infections of the hand often lead to recurrent episodes of erysipelas. This condition should be treated vigorously to prevent marked aggravation of the lymphedematous arm Rigid hygiene of the hands is an essential in prophylaxis.

Weight reduction is also advisable in obese patients and the postoperative tendency to over-eat should be strictly curtailed The postoperative use of a continuous (elastic) bandage or elastic sleeve to the arm has been recommended and successfully used for both prevention and treatment Graded arm exercises are beneficial if used in moderation. Excessive use may improve the function but aggravate the swelling of the post mastectomy arm The spreading factor hyaluronidase has been used by the author but without success A series of patients injected locally in the lymphedematous arm with this enzyme showed only transient improvement

Surgical Measures

The large number of operations designed to achieve a reduction in the size of the swollen arm attest to the fact that no single surgical measure has yet been developed to successfully cope with this problem The operative procedures described in the surgical literature have been collected and classified by Treves (25) who has long been interested in this problem These proposed procedures are grouped as follows (after Treves)

1 Operations designed to increase the return of lymphatic flow by augmenting existing channels and providing for new ones
   a Kondoleon s operation
   b Handley s lymphangioplasty
   c Beck s operation
2 Skin pedical fusion of the lymphedematous arm with the chest wall
   a Standard s operation.
3 Resection of the axillary vein
   a Neuhof's operation
   b Macdonald s operation
4 Stellate ganglion block.
   a Hanelin, Williams Wolfson and Wernick's procedure
5 Homologous muscle transplant in radical mastectomy
   a. Pectoralis minor muscle used to protect the neurovascular structures
      1) Peck and White s method
      2) Murphy s method (quoted by Heyd)
   b Latissimus dorsi muscle used to obliterate the axillary dead-space and protect the neurovascular structures
      1) Rienhoff's method
      2) Moore and Harkins method
   c Teres major muscle used to eliminate axillary dead-space splint neurovascular bundle and provide a tissue bridge for regenerating lymphatics.
      1) Treve's method
6 The use of gelfoam rolls to eliminate axillary dead-space and protect axillary structures.
   a Treve's method
7 Extensive resection to muscle with free skin grafts.

These varied and unique therapeutic techniques have all been employed at one time or another for the relief of postmastectomy lymphedema Their success has been limited and their benefit transient When total disability of the arm or excruciating suffering demand drastic treatment amputation itself has been a refuge of last resort This heroic treatment for massive lymphedema is rarely required but may be indicated for the alleviation of agonizing

pain or the relief of an immensely swollen arm Nevertheless, when there is still a choice of therapy, it is well to temper the treatment before yielding to amputation A sacrifice of this magnitude is often a poor compromise, hoping for comfort and the preservation of life but ending with the loss of both

Massive lymphedema is an uncommon but serious postmastectomy complication which has resisted most efforts at surgical therapy Patients with a large and painfully swollen arm are physically and psychologically handicapped Efforts to surgically correct this condition are intimately linked with those eponymic operations described above, as well as with other original investigators such as Lisfranc, Lexor, Sistrunk, Ghormley, Homans, Matas, Holman, Macey and Pratt But the wheels of surgical progress grind slowly, and the principles of prevention remain, at present, our highest hope In radical mastectomy, "we promise according to our hopes, and perform according to our fears"

Postoperative Rehabilitation

Prostheses

Early in the period of convalescence it is desirable to interest the patient in prostheses and brassieres Some hospitals have added a study of rehabilitation to their nursing curriculum and have special personnel trained in this delicate problem of intimate human relations However, almost all patients first seek the advice of their surgeon concerning the earliest time that a brassiere may be worn and what type of prosthesis is recommended as most satisfactory Although many surgeons may regard this duty as troublesome and time-consuming, patients consider it an obligation rightly within the professional province

Occasionally, a convalescent patient who has recently had a similar breast operation may be of considerable help in facilitating the psychological adjustment of the hospitalized patient Group rehabilitation therapy has also been tried with some success in large surgical centers In these groups women with identical postoperative breast problems have an opportunity of gathering together to discuss quite freely such subjects as cosmetic appearance, proper posture and arm exercises, artificial breast forms and brassieres and the all-important matter of feminine fashions

All surgeons recognize the importance that women attach to their attractiveness and appearance This consideration is of prime concern to most women Therefore, a comfortable and well-fitting prosthesis should be recommended as early as possible during the period of rehabilitation The sooner that patients resume their normal interests, apperance and activities, the more rapid and complete will be their physical and mental rehabilitation As soon as the bulky pressure dressings are removed, the patient should be instructed to wear her regular brassiere, adapting it temporarily with a gauze covered filler of cotton or lamb's wool This can be worn until the wound healing is complete, at which time the patient can then be fitted with a suitable breast substitute This simple device improves the patient's morale and gives the customary normal support to the opposite breast

There are numerous types of brassieres which are commonly sold that are specially designed for postmastectomy patients They are available at local department stores, specialty shops, corsetieres and surgical appliance stores The kind of prosthesis or filler purchased is usually a matter of personal preference Patients can choose from a wide variety of well-fitting appliances such as sculptured sponge rubber, kapok, air-filled forms and a particularly life-like form of balanced weight and natural contour This very satisfactory breast form is made of a

heavy silicone gel filled double layered plastic material Experienced representatives and tactful salesladies are usually available to assist the patient in either custom fitting or the selection of a comfortable standard model Several excellent booklets have been published recently (17 22) which were specifically written for the patient and designed to assist these women in achieving maximum rehabilitation These inspired pamphlets discuss helpful hobbies and feminine fashions for the postmastectomy patient as well as offer many other helpful and hopeful hints

The surgeon s role in rehabilitation is a most important part of total therapy Although certain patients may require more care than others it is obvious that every patient should be given a generous amount of time and attention postoperatively It is the surgeon s duty to be considerate and attentive even though this often requires a great sacrifice of time Many patients quite naturally fear the loss of the remaining breast and often experience sympathetic or phantom breast pains Unnecessary anxiety can be avoided by simple explanation and reassurance Minor postoperative discomfort numbness of the arm and chest wall swelling of the arm or incidental wound complications can be quite simply explained thus giving comfort merely by a surgeon s soothing word or a few extra minutes of re-examination or explanation

Women are naturally curious about their ability to resume their homely chores domestic duties outdoor activities and future husband wife relationships. These thorns of conflict can be quickly set to rest by the wisdom of an experienced surgeon

Many patients require to be cautioned against gaining excessive weight during this postoperative period of restricted activity and mental tension Obesity can become a major problem at this particular time Rehabilitation requires patients to face their problems courageously and without fear or undesirable secrecy Surgeons serve this purpose best by sowing the seeds of self confidence

Exercises

Early in convalescence patients should be encouraged to use but not abuse their arm Routine arm exercises can be begun usually on about the seventh to tenth postoperative day These exercises are to be started slowly and for short periods of time and gradually increased This labor is its own reward Some simple exercises which can be safely recommended are the following

1 **Hair Dressing Exercise** Combing and brushing the hair allows the patient to improve her appearance while elevating her upper arm and making use of her hand and forearm Patients are urged to practice these exercises faithfully with the knowledge that their wound is well healed and cannot be injured by using the arm muscles

2 **Wall Climbing Exercise** (fig 119) The patient is instructed to stand facing a wall She places her fingers against the wall at shoulder level The fingers are used to slowly walk" the arms well over the head This exercise may also be performed by having the patient face at right angles to the wall The arms are then elevated as high as possible and the level is marked on the wall This is repeated several times a day with the object of increasing the height of each marking

3 **Rope Turning Exercise** (fig 120) The patient is told to tie a piece of clothesline six feet long to the knob of a door Taking the loose end of the rope in her hand on the operated side she is instructed to turn the rope with a rotating shoulder motion The speed and size of the circle of this rope turning exercise is gradually increased always using a rigidly extended arm

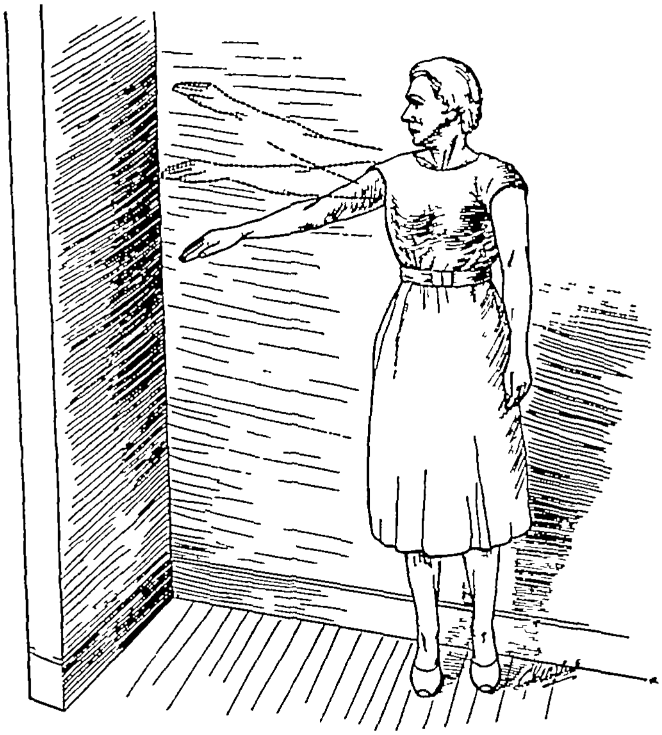

FIG 119 Wall climbing exercise The patient elevates her arm as high as possible marking the level on the wall This is repeated several times a day with the object of increasing the height of each marking (after Radler (22))

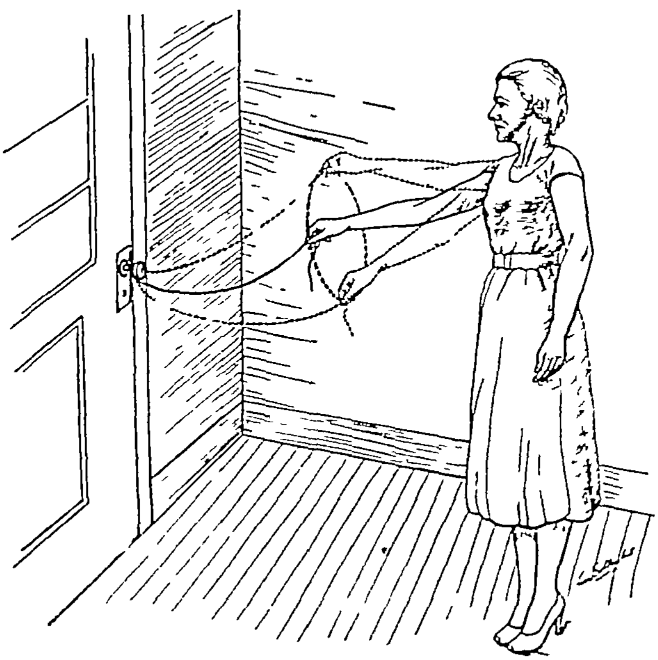

FIG 120 Rope turning exercise The patient is instructed to turn the rope with a rotating shoulder motion The speed and size of the circle is gradually increased (after Radler (22))

4. Pulley Motion Exercise (fig. 121). The patient places a long rope over a shower-curtain rod With the ends of the rope held in each hand the arms are fully extended sideways The rope is then slid up and down pulley-fashion over the rod

Domestic duties of bed-making, sweeping, cleaning* and cooking are to be encouraged when the patient returns home, but heavy lifting or excessive use of the postoperative arm with limited capacity is to be avoided A rapid return to the normal way of life is most desirable Although it is unwise to focus the patient's attention on the use of her arm, it is well to suggest that she should ultimately use it as well as before her operation.

Follow-up

Careful follow-up of all patients with breast cancer is an essential part of the postoperative program An excellent manual prepared by the Cancer Committee of the American College of Surgeons (4) explains this program in detail This is not merely a matter of academic interest but a problem of proper professional care—providing the best possible treatment *at the earliest possible time* for those patients who may develop recurrent breast cancer Sustaining the well-being of the cancer patient can best be accomplished by regular follow-up examinations In the *total* care of patients who have undergone radical mastectomy, it has been our practice to re-examine these patients once every two months for the first year, once every three months for the second year, and increase the interval by one month a year until the patient reaches the six month period Thereafter, the patient is examined regularly once every six months

A rigid follow-up program of this order will require the surgeon to collaborate closely

* Dr William Mendelsohn suggested a very useful exercise consisting of arm sliding as in mirror cleaning

FIG 121 Pulley motion exercise The patient slides the rope up and down with the arms fully extended (after Radler (2?))

with the oncologist and the radiotherapist in the supervision and treatment of local recurrences metastases and/or terminal disease The performance of these humane duties may sometime seem to be an unpleasant chore requiring particular skill perseverance and patience. However there are few sufferings which a sympathetic surgeon can not make lighter (see Chapter VII) In cancer, there are as important lessons to be learned from the short term survivals as from the long term successes The responsibility of the modern surgeon has changed in recent times and as noted by Dunphy (9) the role of the surgeon is that of the key member of a team which consists of the radiologist the oncologist the family physician and the patient s family all of whom must maintain a continued interest in the control of cancer in a given patient whether the disease appears to be arrested has recurred or is obviously spreading widely The surgeon if he is interested in the management of cancer (and if he is not, he should not attempt the mere amputation of an organ) is the key person in the management of the disease and will remain so as long as surgery offers the only definitive hope of permanent or long term arrest of this disease '

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CHAPTER XIV

Prognosis

Introduction

Prognosis in breast cancer is influenced by many factors in addition to the type of therapy. The effects of these influences are subtle and difficult to measure. Contemporary opinions concerning the local origin and subsequent spread of breast cancer indicate than an interval of time does exist in this disease between the period of onset and the ravages of spread. However, the length of this interval prior to metastases varies, and the precise period in each patient is unknown. One can never predict with certainty that therapy will be either curative or hopeless. If we are to evaluate the best treatment methods and to assess the survival results with accuracy, it is necessary to consider the natural history of breast cancer and the factors which influence its prognosis.

Duration of Life in Untreated Breast Cancer

The ultimate result sought in the therapy of breast cancer, as aptly expressed by Shimkin (66), is the permanent eradication of the mammary malignancy and the recovery of the patient. If a "cure" is not possible, then the goal to be achieved is retardation of tumor growth with the prolongation of a useful and comfortable life. If prolongation of life is not possible, then the therapeutic aim should be directed toward the palliation of all distressing signs and symptoms, particularly the relief of pain.

The distinction between curative and non-curative types of therapy is usually quite sharply defined in the case of breast cancer. The clinical indication for radical mastectomy or any other type of curative therapy rests upon the valid statistical demonstration that a significant proportion of patients are alive and well at the end of a fixed period of time, as compared with the inexorable death toll occurring among untreated patients, death being due, of course, to the natural history of the disease. The distinction between therapeutic procedures designed merely to retard the progress of breast cancer and the purely palliative measures are usually less well defined.

Shimkin points out that "statistical analysis of final results on sufficient numbers of adequately controlled cases is the only method by which prolongation of life or cure can be acceptably substantiated." This, quite naturally, involves a comparison of a large series of treated patients with a similar series of untreated controls.

Information regarding the natural history of untreated breast cancer has been collected and reported in the medical literature from many countries. Despite the obvious limitations and intrinsic errors of determining the exact date of onset in cases of breast cancer, the collected data for duration of disease have a definite place of medical importance. The most comprehensive and reliable early studies on the subject of the natural duration of cancer were published by Major Greenwood (21), using British data collected by

TABLE 48

Natural History of Untreated Cancer

Site	No of Cases	Mean Age at Onset	Mean Duration of Disease
		years	*months*
Breast	651	57	38
Rectum	887	55	27
Cervix	1,749	48	21
Oral Cavity	369	57	17
Stomach	154	52	17
Larynx	129	52	15
Esophagus	299	55	12

After Greenwood (21) 1926

Lazarus-Barlow and Leeming (42), Wyard (82) and others, from 1882 to 1924 Similar statistics were reported in London by Forber (17) and in the United States for a later period by Nathanson and Welch (54)

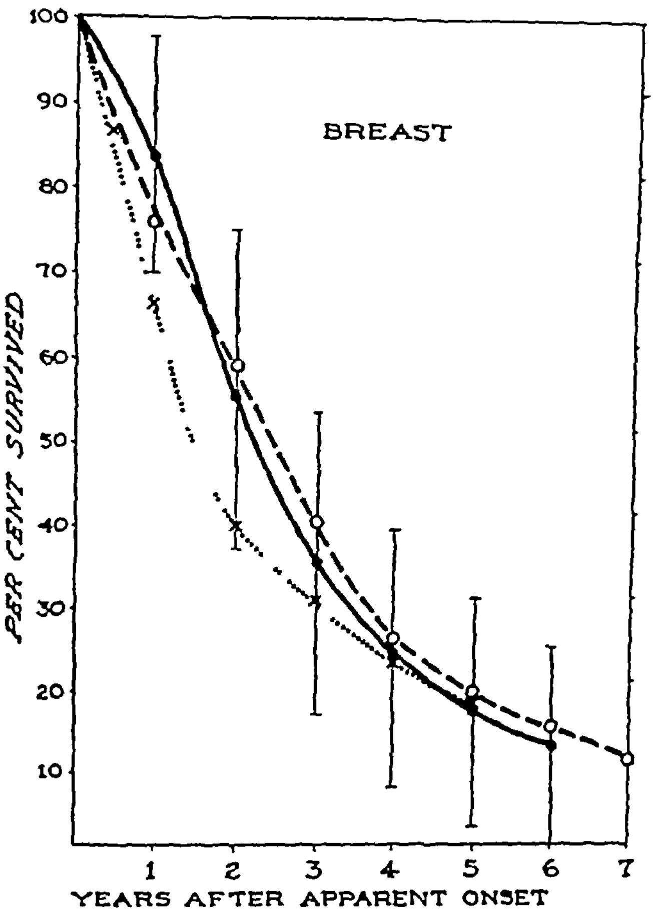
The duration of life in untreated cancer of seven sites (from apparent date of onset to date of death) is summarized in table 48 (after Greenwood)

This data for breast cancer portrayed in graphic form and combined with similar statistics from Forber and Nathanson and Welch is shown in fig 122 (after Shimkin) There appears to be a rather close agreement between these three sets of data derived from different geographical regions and covering varying time periods from 1882 to 1935 The validity of the results by virtue of their similarity alone is thereby enhanced

In a classic study of untreated cancer of the breast, Daland (84) selected one hundred case histories from the Huntington Hospital and the House of the Good Samaritan in Boston None of these patients had received radiotherapy, radium or any surgical procedure including biopsy The duration of life was computed from the first symptom noted by the patient To compare treated and untreated cases, as recognized by Daland, both series must be studied in the same way—from the date of onset of the disease and not from the date of the first examination The average duration of life in this series was 40 5 months, the mean duration was thirty months

As compared with the survival time of Daland's untreated series, Keyes, Orahood and Blumenthal (85) reported a specially selected series to be similarly treated by means of radical mastectomy, in which the average survival span was 73 months The conclusions of these authors indicated that radical mastectomy "significantly prolonged life" when cancer had not advanced locally

One of the most important points to be carefully considered in the natural history of breast cancer is the number of untreated or inadequately treated patients who may survive for unusually long periods of time (table 49) On occasion a woman with a



——— (Greenwood)
- - - - (Nathanson and Welch)
(Forber)

FIG 122 Duration of life from the onset of disease to death in untreated cancer of the breast The vertical lines are probable errors of the means of Greenwood's data (After Shimkin (66) 1951)

TABLE 49

Long Term Survival with Ultimate Recurrence or Metastases

Reported by	Primary Breast	Recurrence	Metastases	Time P O
Gougerot et al (1948)	Case	Locally	—	10 yrs
Hartmann (1942)	4 cases	Locally	—	10 yrs
Hartmann (1942)	3 cases	—	Elsewhere	10 yrs
Hartmann (1942)	Case	Locally	—	11 yrs
Effreduzzi (cit Chilko) (1942)	Case	Locally	—	11 yrs
Brown (1946)	Case #2	Locally	Other breast axill l nodes	11 yrs 6 mo
Uffreduzzi (cit Chilko) (1942)	Case	Locally	—	12 yrs
Hartmann (1942)	3 cases	Locally	—	12 yrs
Hartmann (1942)	Case	Locally	—	13 yrs
Brown (1946)	Case #1	Locally	Axill l nodes	14 yrs
Mortons	Case	Locally	General	14 yrs
Chilko et al (1942)	Case	—	Pleura pericardium med l nodes	15 yrs
Huguenin and Gillet (1939)	Case	Multiple nodules	—	15 yrs
Hartmann (1942)	Case	Locally	—	15 yrs
Hartmann (1942)	Case	—	Elsewhere	16 yrs
Uffreduzzi (cit Chilko) (1942)	Case	Locally	—	16 yrs
Mortons	Case	Locally	Skin shoulder	16 yrs
Gordon Taylor (1939)	Case #5	Locally	—	16 yrs
Gordon Taylor (1939)	Case #4	Locally	—	17 yrs
Gordon Taylor (1939)	Case #6	Locally	—	17 yrs
Hartmann (1942)	2 cases	—	Elsewhere	17 yrs
Powers (1910)	Case	Locally	—	17 yrs, 6 mo
Hartmann (1942)	2 cases	—	Elsewhere	20 yrs
Mitchell (1952)	Case	Locally	—	20 yrs
Flearra (1952)	Case	—	Generalized	20 yrs
Ransohoff (cit Powers) (1910)	Case	Locally	—	21 yrs
Gordon Taylor (1939)	Case #1	Locally	—	21 yrs
Gordon Taylor (1939)	Case #2	Locally	—	22 yrs
Josephy (1951)	Case	—	Elsewhere	22 yrs
Gordon Taylor (1939)	Case #3	Locally	—	23 yrs
Potherat (cit Hartmann) (1942)	Case	Locally	—	23 yrs
Daland (1945)	Case #2	Locally (22 ops) many times	—	24 yrs
Tod and Dawson (1936)	Case	Locally	Opp breast and axilla	24 yrs
Perry (1948)	Case	—	Int mamm l nodes mediastinum pleura gall bl adrenals	27 yrs
Boeckel (cit Perry) (1948)	Case	Locally	—	29 yrs
Mortons	Case	Locally	—	29 yrs
Verneuil (cit Perry) (1948)	Case	Locally	—	30 yrs
Hourtaux (cit Perry) (1948)	Case	Locally	—	30 yrs
Wallace (cit Gordon Taylor) (1930)	Case	—	Pelvic	30 yrs
Steward (cit Gordon Taylor) (1930)	Case	Locally	—	31 yrs
Bowlby (cit Gordon Taylor) (1930)	Case	Locally	—	31 yrs
Halsted (cit Lewis & Rienhoff) (1932)	Case	—	Liver	32 yrs
Mayo and Fergeson (1952)	Case	Multiple local (10 ops)	—	32 yrs
Daland (1945)	Case #1	Locally	Elsewhere	34 yrs, 6 mo
Davidson and Ratcliffe (1946)	Case	—	Elsewhere	40 yrs
Chauffard (1932)	Case	Locally	—	50 yrs

After Morton and Morton (53) 1953

verified breast cancer will resort to a unique therapeutic regimen and by implication alone will attribute her long-term survival to the protective charm of some occult remedy. Explicit knowledge of the natural history of breast cancer with its rare instances of spontaneous regression or long-term periods of quiescence and survival emphasize the extreme caution that must be exercised in this disease in the evaluation of the effect of any form of therapy in each individual patient.

Duration of Life in Treated Breast Cancer

Advancement of the Disease

Despite the vast medical literature which has been only briefly reviewed in Chapter X, it is readily apparent that the postoperative survival of patients with breast cancer is dependent upon many varied factors. The difficulty of precisely evaluating these factors is inherent in the science of statistics which has become, as noted by the British Medical Journal (13), "vastly elaborate, and the exclusion of disturbing variables is an advanced mathematical exercise. Consequently, a statistical analysis presents a structure so intricate, so specialized, and so formidable that this complicated erection has to be taken to pieces by an expert before a flaw can be detected in some small piece of the mechanism, upon which the whole working depends." To surgeons, therefore, statistics are neither sacred nor profane but merely regarded with some reserve especially as they pertain to arguments alleging one method of treatment to be superior to another. While exact statistical data must be used to measure comparative differences in treatment and survival, yet the reaches of statistical science have their limits. Perhaps the basic human material which is the key to biostatistics is not sufficiently tempered with known facts to fulfill the difficult task which it is called upon to perform.

Modern statistical research has, however, rendered surgery a service by ruffling the feathers of current complacency regarding the expectations from several types of surgical therapy. The selective limitations of radical mastectomy must be appreciated and alternative modes of treatment in certain cases then will come to be regarded in a more favorable light. This will create an eclectic attitude toward the problem of breast cancer and its treatment.

Although our ultimate hopes may rest with the endocrinologist, the virologist or the experimental chemotherapist, yet in the surgical treatment of breast cancer our current strategy is based upon the belief that there is a stage when, apart from a few stray cells which may lie dormant within the embrace of the body defenses, the growth of malignant cells is confined to the breast and accessible regional nodes. The classic Halsted radical mastectomy provides a rampart of preservation for these patients. Whereas differences in survival between modes of surgical therapy might be very small and might require the most careful statistical analysis to reveal them, yet these very small differences are of supreme importance to the individual patient who survives.

A long-term follow-up survey of all patients with primary breast cancer who received surgical treatment at the Johns Hopkins Hospital during the period 1935 to 1940 inclusive was reported by Lewison, Trimble and Griffith (49). A total of 255 patients, both private and ward, Negro and white, entered the hospital with a clinical diagnosis of breast cancer. Two hundred and twenty of these patients subsequently underwent operation, 14 were treated by simple mastectomy, 204 by radical mastectomy and two by local excision (one patient having pulmonary metastases and the other refusing

TABLE 50

Five Year End Results of Surgical Treatment for Breast Cancer at the Johns Hopkins Hospital (1935–40)

Type of Treatment	Stage of Disease	Number of Patients	Living and Well		Living with Recurrence		Total Survivors	
			No	Per cent	No	Per cent	No.	Per cent
Radical mastectomy	Breast alone	78	44	56 4	6	7 7	50	64 1
	Breast and axilla	126	35	27 7	5	4 0	40	31 7
Total		204	79	38 7	11	5 4	90	44 1
Simple mastectomy	Breast alone	5	2	40 0	—	—	2	40 0
	Breast and axilla	9	2	22 2	—	—	2	22 2
Total		14	4	28 6	—	—	4	28 6
Local excision	Breast alone	1	1	100	—	—	1	100
	Breast and axilla	1	—	—	—	—	0	0
Total		2	1	50	—	—	1	50
Total		220	84	38 2	11	5 0	95	43 2

further treatment) The remaining 35 patients were treated either by radiotherapy alone, were considered to have lesions hopelessly advanced and beyond treatment were discharged without treatment or refused treatment.

A successful follow up was obtained in 208 patients, or 94.5 per cent of the series All patients lost to follow up or those dying of intercurrent disease were considered dead of breast cancer for the purpose of this computation

The presence or absence of axillary node involvement is of paramount importance and of decisive influence in predicting the prognosis of patients with breast cancer Table 50 records the five-year survival rate at the Johns Hopkins Hospital for (1) those patients without axillary metastases by microscopic examination (64 1 per cent five year survival) and (2) those patients with axillary metastases by microscopic examination (31 7 per cent five year survival)

The total five year survival rate for all patients regardless of the type of surgical treatment or the stage of the disease was 43 2 per cent The so-called clinical cure' rate—patients living and well without discernible evidence of recurrence of metastases at the end of five years—was 38.2 per cent. Axillary metastases were noted in 62 per cent of patients who were subjected to radical mastectomy When surgical treatment consisted of radical mastectomy almost two thirds of the patients without axillary metastases were still alive five years after operation whereas only one third of the patients with axillary metastases were alive at the end of this period

The ten year end results of surgical treatment are shown in table 51 The over all ten year survival rate for this hospital was 29 1 per cent If cancer remained confined to the breast alone however the ten year survival rate was 47 6 per cent. On the other hand if breast cancer had already spread to the adjacent axilla, the ten year survival rate fell to 17 6 per cent The importance of

TABLE 51

Ten Year End-Results of Surgical Treatment for Breast Cancer at the Johns Hopkins Hospital (1936–40)

Stage of Disease	Number of Patients	Living and Well		Living with Recurrence		Total Survivors	
		No.	Per cent	No.	Per cent	No.	Per cent
Breast alone	84	34	40.5	6	7.1	40	47.6
Breast and axilla	136	23	16.9	1	0.7	24	17.6
Total	220	57	25.9	7	3.2	64	29.1

metastases to the regional nodes in the prognosis of breast cancer, therefore, is obviously of salient significance.

Harrington (31) has presented the fifteen year to forty year survival rates for breast cancer following radical mastectomy performed at the Mayo Clinic. Whereas no method of predicting the prognosis is valid in any individual case, the factors of importance in the prognosis of breast cancer as indicated by Harrington are as follows:

1. The extent of the malignant involvement at the time of operation.
2. The degree of malignancy as shown by microscopic examination of the primary tumor.
3. The presence of such associated conditions as pregnancy and lactation.
4. The presence of constitutional diseases such as diabetes.

The most important of these factors is the extent of the disease at the time of operation as indicated by the presence or absence of axillary nodal metastasis found microscopically at the time of operation. The prognosis is decidedly more favorable in patients in whom the axillary lymph nodes are not involved by metastatic spread than in those patients in whom axillary spread is found to be present at operation.

An important factor in prognosis is the natural resistance of the tissues of the host to the growth and spread of cancer. There is no known method of evaluating this property of normal tissues to resist malignant disease. However, host resistance must vary from time to time and from one person to another. It may inhibit the invasiveness and extension of the primary tumor locally, as well as act as a restraint to the more distant metastatic dissemination of breast cancer.

There were 4,637 patients who underwent radical mastectomy at the Mayo Clinic from 1910 through 1934 and of these there were 4,563 patients (98.4 per cent) who were successfully traced. The 15 to 40 year survival rates of these traced patients are summarized in table 52.

It is indeed gratifying to note that 25.1 per cent of all patients operated upon by

TABLE 52

The 15- to 40-Year Survival Rate Following Radical Mastectomy for Unilateral Breast Cancer in the Female

Years P.O.	Patients		Lived Indicated Period	
	Total	Traced	No.	%*
15 or more	4,637	4,563 (98.1%)	1,141	25.1
20 or more	3,615	3,544 (98.0%)	621	17.6
25 or more	2,439	2,391 (98.0%)	301	12.6
30 or more	1,415	1,375 (97.2%)	128	9.3
35 to 40	520	507 (97.5%)	35	6.6

* Based on traced patients. Inquiry as of January 1, 1950.

After Harrington (31) 1953.

TABLE 53

*Unilateral Carcinoma of the Breast (Females) With and Without Nodal Metastasis Survival Rates 15 to 40 Years Following Radical Mastectomy**

Years P.O	With Metastasis (63 7 Per Cent)				Without Metastasis (36.3 Per Cent)			
	Patients		Lived indicated period		Patients		Lived indicated period	
	Total	Traced	No.	%	Total	Traced	No.	%
15 or more	2 953	2 918	351	12 0	1 684	1 645	793	48 2
20 or more	2 336	2 302	172	7 5	1 279	1 242	452	36 4
25 or more	1 560	1 538	73	4 7	879	853	228	26 7
30 or more	898	884	34	3 8	517	491	94	19 1
35 to 40	304	300	6	2 0	216	207	29	14 0

* Based on traced patients Inquiry as of January 1 1950
After Harrington (31) 1953

means of radical mastectomy almost a generation ago survived 15 years or more

The important influence of axillary metastases on prognosis, as noted at the time of operation is indicated in the survival rates shown in table 53

There is considerable difference in the survival rates in each five-year postoperative period (table 54) between patients with and without axillary metastases. This noteworthy difference in prognosis has been found to be universally true

The stage of advancement of breast cancer at the time of the first treatment is by far the most important single factor in assessing prognosis. The variation in the five year survival rate from 80 to 90 per cent in those patients with early Stage I cancer to five per cent or less in patients with widespread metastases (Stage IV) exceeds that of any other known factor influencing prognosis. The results of treatment of breast cancer when the disease is considered by clinical stages have been reviewed in Chapter X. The prognosis in relation to stage of advancement of the disease at the time of

TABLE 54

Five Year Survival Rates After Radical Mastectomy During Different Five Year Periods

Period of Operation	With Metastasis			Without Metastasis			Total		
	No. traced	No.	%	No. traced	No.	%	No. traced	No.	%
1910–1914	303	71	23 4	214	134	62 6	517	205	39 7
1915–1919	592	155	26 2	294	210	71 4	886	365	41 2
1920–1924	659	156	23 7	360	252	70 0	1 019	408	40 0
1925–1929	762	248	32 5	399	308	77 2	1 161	556	47 9
1930–1934	612	216	35 3	403	329	81 6	1 015	545	53 7
1935–1939	662	268	40 5	589	482	81 8	1 251	750	60 0
1940–1944	741	292	39 4	735	629	85 6	1 476	921	62 4
Total	4 331	1 406	32 5	2 994	2 344	78 3	7 325	3 750	51 2

After Harrington (30) 1952

TABLE 55

Stage	No of Patients	5 Year Actuarial Survival Rate	Standard Error
		per cent	*per cent*
I	165	74 1	3 49
II	242	53 4	3 30
III	224	23 6	2 99
IV	138	8 8	2 46
Unstaged	54	52 0	6 98

After Smithers et al (1952)

treatment have been reported for the Royal Cancer Hospital by Smithers et al. (71) in table 55

Extent of Axillary Metastases

Although the most important factor in predicting the postoperative survival of patients with breast cancer has proved to be the presence or absence of metastases to the axillary or other accessory regional lymph nodes, there has been relatively little interest shown in the degree of this axillary lymph node involvement Warren and Tompkins (78), in a small series, have carefully exploited the prognostic value of *extent* in the pathological examination of axillary lymph nodes in breast cancer The discrepancy between the clinical and pathologic findings of axillary involvement may introduce an error of considerable magnitude (see Chapter VIII), and therefore the clinical estimate of extent of axillary metastases must be cautiously viewed with some doubt and uncertainty

Coller, Kay and MacIntyre (6) and Davis and Neis (8) have shown that by special clearing techniques a substantially greater number of lymph nodes can be discovered than by the usual methods of examination and that metastases occasionally occur in the small easily overlooked nodes Saphir and Amromin (63) found a substantially higher incidence of obscure axillary lymph node metastases by a technique of serial sections Metastatic cancer was found in 33 3 per cent of instances in which previous examination had not disclosed tumor in the nodes While clearing techniques, serial sectioning and the classifying of axillary nodes into apical, middle and basal groups might give more accurate data, these methods are time consuming, expensive and generally unsuited for routine use However, a careful search of the gross specimen indicating total number of nodes found and number containing metastases is an important part of the surgical-pathologic routine

The extent of involvement of axillary lymph nodes reveals that survival is inversely proportional to the number of axillary nodes containing metastases

Curability, as well as survival time of patients ultimately dying of the disease, decreases as the extent of *metastases to the* axillary lymph nodes increases Local recurrence is also apt to increase with greater axillary involvement This increased incidence *rrence, as noted by Warren* gests that skin recur- ive area may not be al implants Subcu- ension

TABLE 56

Effect of Extent of Axillary Metastases on Survival

	No Cases	Living and Well at 5 Years
		%
No metastases to axillary lymph nodes	81	85
Metastases involving less than 50 per cent of axillary nodes	22	68
Metastases involving more than 50 per cent of axillary nodes	31	
Metastases involving 100 per cent of axillary nodes	37	

After Warren and Tompkins (78

of the primary disease may also account for these apparent regional recurrences

The poor prognosis generally given in a case where only a few axillary nodes are involved is probably unwarranted Those patients with metastases to only one or two nodes out of many uninvolved axillary nodes may have almost as good a chance for prolonged survival as those patients with no axillary metastases Moreover patients with most or all of their axillary nodes involved by cancer not only have a much poorer prognosis for life itself but also their period of postoperative survival is considerably shortened A corollary to these conclusions, of course concerns operative technique The greater the number of axillary lymph nodes removed by a carefully performed radical mastectomy the greater the chances of survival and the more accurate the prognosis.

Histologic Grading and Prognosis

Opinions of clinicians and pathologists vary widely regarding the prognostic value of histologic grading in cancer of the breast Von Hansemann (76) in 1893 is said to have been the first to introduce the concept of anaplasia and to attempt to correlate the histologic appearance of cancer with its clinical behavior However only scanty attention was paid to tumor grading until Broders (4) revealed a significant relationship between anaplasia and survival Greenough (20) shortly thereafter studied the grade of malignancy of breast cancer and reported a parallel between the histologic picture and prognosis. Cellular differentiation and other cytologic criteria were considered by MacCarty (51) to be most important factors in the prognosis of breast cancer

However differences of opinion regarding the accuracy of histologic grading as an index of survival have varied from those who found as many as 20 characteristics of prognostic value to those who were unable to find even one Reimann (60) concluded that it was futile to decide from an examination of the microscopic section what will happen to the patient Plaut (59) in a careful review of the literature concluded that he could not advocate the method of histologic grading as an index of prognosis. Willis (81) believes that the precise numerical grading of malignancy is arbitrary and of little practical value Broad grouping based upon general histologic structure may be helpful

Warren and Tompkins (78) do not ordinarily grade breast cancers because the personal equation in the process is too great This is particularly true of the intermediate grades. There is of course a real need for some reliable method of assessing the degree of malignancy from a study of breast cancer histology If histologic grading of biopsy specimens could only provide a more precise prognostic picture it would certainly be of greater value than the vague statements of duration of disease or inaccurate clinical measurements of tumor size or site upon which we are forced to rely

Tumor grading however is not without its serious difficulties. One small biopsy specimen may not be representative of the entire tumor and metastases are not necessarily the image of their primary progenitor As noted by Richards (61) tumor grading thus far has proved to be only partially satisfactory An excellent survey of this problem has been presented by Bloom (2) who advocates that prognosis be based upon tumor grading taken together with tumor staging (axillary lymph node metastases) as the most accurate indication of survival presently available Clinical staging plus histological grading was of greater prognostic value than either method alone This combined clinicopathological system for deter

TABLE 55

Stage	No of Patients	5 Year Actuarial Survival Rate	Standard Error
		per cent	per cent
I	165	74 1	3 49
II	242	53 4	3 30
III	224	23 6	2 99
IV	138	8 8	2 46
Unstaged	54	52 0	6 98

After Smithers et al (1952)

treatment have been reported for the Royal Cancer Hospital by Smithers et al. (71) in table 55.

Extent of Axillary Metastases

Although the most important factor in predicting the postoperative survival of patients with breast cancer has proved to be the presence or absence of metastases to the axillary or other accessory regional lymph nodes, there has been relatively little interest shown in the degree of this axillary lymph node involvement Warren and Tompkins (78), in a small series, have carefully exploited the prognostic value of *extent* in the pathological examination of axillary lymph nodes in breast cancer The discrepancy between the clinical and pathologic findings of axillary involvement may introduce an error of considerable magnitude (see Chapter VIII), and therefore the clinical estimate of extent of axillary metastases must be cautiously viewed with some doubt and uncertainty

TABLE 56

Effect of Extent of Axillary Metastases on Survival

	No Cases	Living and Well at 5 Years
		%
No metastases to axillary lymph nodes	81	85
Metastases involving less than 50 per cent of axillary nodes	22	68
Metastases involving more than 50 per cent of axillary nodes	31	38
Metastases involving 100 per cent of axillary nodes	37	19

After Warren and Tompkins (78)

Coller, Kay and MacIntyre (6) and Davis and Neis (8) have shown that by special clearing techniques a substantially greater number of lymph nodes can be discovered than by the usual methods of examination and that metastases occasionally occur in the small easily overlooked nodes Saphir and Amromin (63) found a substantially higher incidence of obscure axillary lymph node metastases by a technique of serial sections Metastatic cancer was found in 33 3 per cent of instances in which previous examination had not disclosed tumor in the nodes While clearing techniques, serial sectioning and the classifying of axillary nodes into apical, middle and basal groups might give more accurate data, these methods are time consuming, expensive and generally unsuited for routine use However, a careful search of the gross specimen indicating total number of nodes found and number containing metastases is an important part of the surgical-pathologic routine

The extent of involvement of axillary lymph nodes reveals that survival is inversely proportional to the number of axillary nodes containing metastases

Curability, as well as survival time of patients ultimately dying of the disease, decreases as the extent of metastases to the axillary lymph nodes increases Local recurrence is also apt to increase with greater axillary involvement This increased incidence of local recurrence, as noted by Warren and Tompkins, suggests that skin recurrences in the operative area may not be entirely a matter of local implants Subcutaneous metastases or lymphatic extension

of the primary disease may also account for these apparent regional recurrences

The poor prognosis generally given in a case where only a few axillary nodes are involved is probably unwarranted Those patients with metastases to only one or two nodes out of many uninvolved axillary nodes may have almost as good a chance for prolonged survival as those patients with no axillary metastases Moreover patients with most or all of their axillary nodes involved by cancer not only have a much poorer prognosis for life itself but also their period of postoperative survival is considerably shortened A corollary to these conclusions, of course, concerns operative technique The greater the number of axillary lymph nodes removed by a carefully performed radical mastectomy the greater the chances of survival and the more accurate the prognosis.

Histologic Grading and Prognosis

Opinions of clinicians and pathologists vary widely regarding the prognostic value of histologic grading in cancer of the breast Von Hansemann (76) in 1893 is said to have been the first to introduce the concept of anaplasia and to attempt to correlate the histologic appearance of cancer with its clinical behavior However only scanty attention was paid to tumor grading until Broders (4) revealed a significant relationship between anaplasia and survival Greenough (20) shortly thereafter studied the grade of malignancy of breast cancer and reported a parallel between the histologic picture and prognosis. Cellular differentiation and other cytologic criteria were considered by MacCarty (51) to be most important factors in the prognosis of breast cancer

However differences of opinion regarding the accuracy of histologic grading as an index of survival have varied from those who found as many as 20 characteristics of prognostic value to those who were unable to find even one Reimann (60) concluded that it was futile to decide from an examination of the microscopic section what will happen to the patient Plaut (59) in a careful review of the literature concluded that he could not advocate the method of histologic grading as an index of prognosis. Willis (81) believes that the precise numerical grading of malignancy is arbitrary and of little practical value Broad grouping based upon general histologic structure may be helpful

Warren and Tompkins (78) do not ordinarily grade breast cancers because the personal equation in the process is too great This is particularly true of the intermediate grades There is, of course a real need for some reliable method of assessing the degree of malignancy from a study of breast cancer histology If histologic grading of biopsy specimens could only provide a more precise prognostic picture it would certainly be of greater value than the vague statements of duration of disease or inaccurate clinical measurements of tumor size or site upon which we are forced to rely

Tumor grading however is not without its serious difficulties. One small biopsy specimen may not be representative of the entire tumor and metastases are not necessarily the image of their primary progenitor As noted by Richards (61) tumor grading thus far has proved to be only partially satisfactory An excellent survey of this problem has been presented by Bloom (2) who advocates that prognosis be based upon tumor grading taken together with tumor staging (axillary lymph node metastases) as the most accurate indication of survival presently available. Clinical staging plus histological grading was of greater prognostic value than either method alone This combined clinicopathological system for deter

mining breast cancer prognosis requires careful study and further confirmation

However, as noted by Smithers et al (71), it is the clinician who has to gauge prognosis and decide upon treatment based upon clinical staging of the disease without the benefit of pathologic examination Whereas tumor grading is a reflection of wisdom of action already taken, clinical staging determines the wisdom of action about to be taken

Colcock and Sommers (83) have reviewed the prognosis of Paget's disease of the breast and also have called attention to the difficulties of determining proper treatment Often a surgeon hesitates to carry out a radical mastectomy for what appears to be merely a small cutaneous lesion of the nipple (even if biopsy has confirmed the presence of cancer) This is particularly so when no palpable breast tumor is present The pathologist, realizing that a small impalpable cancer is frequently found beneath the weeping eczematoid nipple lesion, hesitates to recommend anything less than radical mastectomy

There is general agreement that Paget's disease represents an intra-epithelial extension of an intraductal breast cancer which has appeared in the epidermis of the nipple The five-year survival rate in Paget's disease, reported by these authors, was only 30 per cent as compared with a five-year survival rate of 39 per cent for a control series of unselected breast cancer If no palpable mass is present *and* the surgical pathologist finds only an intraductal carcinoma, Colcock and Sommers recommend simple mastectomy However, if a "palpable tumor is present *or* if the pathologist finds invasive carcinoma, a radical mastectomy should be carried out" When invasive carcinoma occurs in Paget's disease the prognosis is regarded as poor

To determine if there might be any notable histologic characteristics peculiar to breast cancer patients with long-term survivals, Lewison, Trimble and Griffith (49) reviewed the histologic sections of 64 patients who were known to have survived ten years or longer This differed from the usual practice followed in histologic evaluation of prognosis where microscopic sections are reviewed without the clinical course being foreknown

In the examination of the sections, the following factors were specially noted 1) lymph node involvement, 2) vessel invasion, 3) pattern, 4) tubule formation, 5) cellular and nuclear morphology, 6) hyperchromatism, 7) mitoses, 8) necrosis and 9) desmoplasia For the most part Stewart's (73) histological classification of breast cancer was used Table 57 shows the variety of histological types, tubule formation and lymph node metastases found in this series of ten year survivals

In general, it may be stated that no histological characteristics that could be correlated with the prolonged clinical course were found in a review of these 64 carcinomas of the breast from women known to have survived ten years or longer There were, however, several results of the study that warrant mention It was notable that in only one case was the diagnosis of in situ carcinoma made, the other 63 cases showing definite stromal infiltration In 24 cases (37 5 per cent) metastases were revealed in one or more lymph nodes Not infrequently other findings also generally regarded as purporting a poor prognosis were noted, such as skin invasion and metastases to muscle Tubule formation indicating a favorable prognosis was absent in 41 (64 per cent) cases, as noted in table 57 It is interesting that adenocarcinoma, "comedo" carcinoma and medullary carcinoma with lymphocytic infiltration, the histological types of duct carcinoma usually associated with a better prognosis, were not

especially conspicuous in this series It is remarkable that the proportion of the histological types of breast carcinoma noted in this long survival series is about the same as the proportion seen for all cases of breast carcinoma. These observations demonstrate that, at least in this series, the histological appearances alone would not have allowed one to prognosticate the favorable ten year survival that ensued

Thus, the outlook for a patient with cancer of the breast depends first and foremost upon the extent of the disease when first discovered Histologic appearance and tumor grading are less important omens of prognosis but may be of ancillary benefit in determining the degree of radiosensitivity other factors being considered

TABLE 57

Histological Classification of Breast Carcinoma in 64 Patients Known to Have Survived Ten Years or Longer

Type	No.	%	Tubules Present	Nodes Involved
Duct carcinoma				
Infiltrating with fibrosis (scirrhous)	26	40 6	12	10
Papillary with infiltration	2	3 1	2	1
Medullary carcinoma with lymphoid infiltration	5	7 9	1	3
Mucoid carcinoma	2	3 1	2	1
Infiltrating comedo type	8	12 5	1	2
Infiltrating carcinoma (mixed or unclassified*)	15	23 0	8	5
In situ duct carcinoma	1	1 5	—	—
Anaplastic carcinoma	2	3 1	—	—
Well-differentiated adenocarcinoma	1	1 5	1	1
Lobular carcinoma	1	1 5	—	1
Equivocal carcinoma†	1	1 5	—	—

* It was not well demonstrated in the sections available that all these arose from ducts but their general pattern was strongly suggestive

† A positive tissue diagnosis of breast carcinoma had previously been made from other sections of the operative specimen than those available at this time

AGE

Considering the cardinal factors which could conceivably modify the survival rate of breast cancer age has been regarded by various investigators as an equivocal index of prognostic significance Many authors contend that age has an important bearing on prognosis. The prevailing impression was voiced by Ewing (15) who stated that before thirty years of age mammary cancer is extremely fatal.' It is a common but debatable doctrine that the younger the cancer patient the less hopeful is the outlook On the other hand Richards, in a critical clinical analysis of survival in 906 cases of breast cancer concluded that there was no justification for the assumption that the prognosis was less favorable in young women merely because of age alone

Yet breast cancer occurring before the age of 30 is frequently considered to be a most ominous disease. Haagensen and Stout (24) indicated that some surgeons consider the condition categorically "inoperable and refuse to perform definitive surgery A special study of breast cancer in young women was undertaken by Lee (43) He investigated 191 cases treated by radical mastectomy all of whom were under the age of 40 The three-year survival rate was only 40 per cent Lee concluded that 'cancer of the breast in young women is a much more menacing disease than it is in mid life or old age In commenting on these poor results Bloom (3) calls attention to the lack of controls among older patients from the same clinic as well as the inclusion of women with more serious lactation cancer in this selected series The ill-effect of pregnancy and lactation on breast cancer is a special

problem which has been separately discussed in Chapter XVII The prognosis for these younger patients in whom pregnancy is a complication is particularly poor

The over-all five year survival rate for breast cancer patients at the Johns Hopkins Hospital was found by Lewison, Trimble and Griffith to be 43 2 per cent However, the five year survival rate computed for patients under the age of 40 was only 29 6 per cent Thus, a comparatively unfavorable prognosis for young women was demonstrated in this small series Yet, it should be carefully noted that the breast and axilla were involved in 61 8 per cent of the entire series Whereas in the limited group of women under the age of 40 the breast and axilla were involved more often, in 70 4 per cent, thus indicating a more advanced stage of the disease at the time of operation

In the case of breast cancer, destiny appears to grant no special favor to the young or to the mothers of the young On the contrary, the view held by Nathanson and Welch (54), Cade (5), Pack and Livingstone (58) and others indicates that the prospects for this group are indeed unpromising

However, there are those who find that age in itself is of little or no prognostic significance In a collected series of 73 breast cancer cases all under the age of 30, de Cholnoky (11) found the five and ten year survival rate to be comparable to that of older age groups Hawkins (33), in an investigation of several thousand cases of breast cancer, concluded that the data did not support the contention that younger cancer patients have any more somber outlook than older patients The five year survival rate in three age groups 1) patients under 49, 2) patients 50 to 59 and 3) patients over 60, were generally comparable

Lane-Claypon (40) demonstrated a similar five-year survival rate among 530 collected cases of breast cancer when considered by decennial age periods "The figures do not bear out the suggestion that there is any inherently greater malignancy in cancer among young persons, unless the growth is allowed to extend beyond the breast, when the results are more unfavorable " In a later study Lane-Claypon (41) analyzed a larger series of cases and divided them into three age groups 1) patients under 40, 2) patients 40 to 59, and 3) patients aged 60 or over From a study of her end-results Lane-Claypon concluded that the prospects for "cure" were certainly no less favorable in young patients with breast cancer than for those nearer the end of their normal physiological life span

In a large series of cases studied at the Mayo Clinic, Harrington (29) found that age alone had no significant bearing on the prognosis The proportion of patients with and without axillary metastases in the majority of age groups appeared comparable

Bloom (2, 3) noted a considerable fluctuation in the prognosis of patients in the several age groups which he studied "No parallel is revealed between age and outcome, and there is no support for the view that the tumours of younger women, apart from those associated with pregnancy and lactation, kill more rapidly "

In an interesting survival study by Richards the cases of breast cancer were grouped in relation to the menopause (table 58) 1) prior to menopause, 2) concurrent with the menopause or up to five years after, and 3) five years after the menopause or longer From a careful examination of the five and ten year survival rates, there appeared to be very little significant difference in the total five year survivals in the three groups If anything, the premenopausal group seemed to have the best prognosis Compounding the caprice of these biostatistics, Richards found that the menopausal group seemed to have the poorest ten year survival rate

Wade (77) in a comparative study of results, found that the survival of 649 women with untreated breast cancer was uninfluenced by age alone. At the Royal Cancer Hospital Smithers and his colleagues found that there was some tendency for prognosis to vary with age, being comparatively good in younger women, being poor in women in their fifties, improving again in the sixties and seventies, and being bad in the aged." In 846 patients treated at the Royal Cancer Hospital the five year survival rate recorded in relation to age when first seen at the hospital is shown in table 59.

Haagensen and Stout (25) have periodically reviewed their end results and have found a comparatively good prognosis for younger patients. Youth or old age are not considered contraindications to radical mastectomy. Since most observers agree that the rate of growth is perhaps slower in the older patient with breast cancer, Haagensen regards these patients as most amenable to surgical therapy: "... we do not hesitate today to perform radical mastectomies on women of advanced age, including those in their eighties, even when they have a considerable degree of cardiovascular disease."

It is the opinion of Geschickter (18) that certain unfavorable biologic features exist for younger women with breast cancer, but as emphasized by Kane (35), these differences may be compensated for by the fact that younger patients tend to seek medical attention much sooner than older patients. This has been also noted at the Radiumhemmet in Stockholm by Nohrman (56). Similarly, Lewison et al. (48) have found that young women are more alert and receptive to the danger signals of breast cancer and to cancer education generally as evidenced by their response to the teaching of breast self-examination.

Small and Dutton (86) have reported the survival experience in a single hospital with complete survival curves rather than five-year survival rates in (1) radically treated and (2) non-radically or untreated breast cancer patients. In both series they noted a high mortality within the first few years. These authors concluded that breast cancer mortality appeared to be a constant process regardless of the type of treatment. Age, however, was considered to be a most im-

TABLE 58

Mammary Carcinoma: Survival in Relation to Menopause

Group	Stage	No. of Cases	5 Year Survival	No. of Cases	10 Year Survival
			%		%
Pre-menopausal	I	68	83	31	65
	II	65	60	36	42
	III	158	46	62	26
	IV	34	15	13	8
	V	15	7	5	0
Total		340	51	147	35
Menopausal	I	31	90	7	43
	II	35	40	18	11
	III	66	29	26	8
	IV	25	16	9	11
	V	4	0	3	0
Total		161	40	63	13
Post-menopausal	I	50	78	18	55
	II	86	58	38	32
	III	173	35	61	18
	IV	80	16	26	7
	V	20	0	4	0
Total		409	40	147	24

General Summary for Comparison: All Cases (1189) —1933–1943

	I	II	III	IV	V	Total
	%	%	%	%	%	%
5-year survival	81	54	28	16	3	43
10-year survival	59	28	21	8	0	26

After Richards (61) 1948

TABLE 59

Age	No of Patients	5 Year Absolute Survival Rate
		%
21–30	4	25 0 (28 3)*
31–40	90	43 3 (44 0)
41–50	199	48 3 (49 7)
51–60	240	29 0 (30 9)
61–70	197	38 1 (44 7)
71–over	116	23 9 (38 5)
Total	846	36 5 (41 1)

* The figures in parentheses are the absolute survival rates corrected for expected number of deaths from other causes

After Smithers (71) 1952

portant prognostic factor in the survival of patients with breast cancer The younger the patient the poorer the prognosis regardless of treatment

Geschickter found the average postoperative duration of life in patients younger than 40 to be 3 45 years, compared to 5 5 years for patients older than 40 Sistrunk and MacCarty (69) noted that 41 7 per cent of patients over 50 years of age were living five to eight years after operation, as compared with only 31 8 per cent of patients under 50 Whereas the five year survival rate may be more or less comparable regardless of age, the rapid termination of tumors which prove to be fatal in the young person seriously shortens the average postoperative period

Those authors who claim that a relationship exists between age and prognosis usually maintain that the breast cancers of younger patients tend to be more anaplastic than do those of older patients If this were true, Bloom (2, 3) suggests that one would expect to find a greater proportion of breast cancers of a highly malignant histologic grade among younger patients However, in a study of age, grade of tumor and prognosis, Bloom found a remarkably even distribution of high and low grade malignancies in the various decades of life Correlating the cytology and histology with age and prognosis in accord with his criteria gave no support to the belief that cancer of the breast is any more malignant in younger patients Whereas these results are in general agreement with those of Lees and Park (46), they are in direct disagreement with the earlier studies of Taylor (74) Using the principles of histologic grading recommended by Greenough, Taylor found a larger number of breast cancers of a high order of malignancy among young women

Thus, the influence of age alone on the prognosis of patients with breast cancer appears to be exceedingly difficult to determine In the realm of biostatistics the simple truth which is often at the mercy of so many nonmeasurable biologic variables may be impossible to verify Therefore, by reviewing the current literature, it is quite possible for sound and reasonable surgeons to hold conflicting points of view regarding the prognostic significance of age in breast cancer The prevailing impression (all extraneous factors being biologically equal) that the younger the patient the poorer the prognosis remains a prophetic imponderable

DURATION OF DISEASE

In many instances of breast cancer a distinction will be evident in the case history between those "lumps" which have appeared suddenly or have had a rapid onset and those which have grown slowly over a long period of time As noted by Richards, tumor size and duration of disease are often expressions of the degree of malignancy which may have an important bearing on ultimate prognosis. Although an accurate history is frequently difficult if not impossible to obtain regarding the true duration of disease, yet full use of all pertinent information concerning time should be made whenever possible A brief history may be indicative of an intelligent

and observant patient anxious to detect an early cancer or on the other hand it may merely reflect fear ignorance or an unobservant patient with an advanced lesion *Data regarding the duration of the disease is dependent upon (1) the patient's memory and (2) upon an innate tendency to tamper with the truth of time in accord with one's fears or the tone of the physician's question*

Interpreted with a certain degree of reservation, the influence of the fundamental factor of 'rate of growth' on survival was studied by Richards in 324 cases of breast cancer (table 60) Accurate data in these patients were presumed to be available The prognosis was found to be most favorable when the rate of growth (or mitotic interval) was slowest

TABLE 60

Rate of Growth vs Survival Mammary Carcinoma 1939–41

Rate of Growth	Total No. of Cases	Alive after 5 Years
		%
Slow (less than 1 cm per 6 months)	55	84
Moderate (1 cm per 6 months)	104	63 5
Fast (more than 1 cm per 3 months)	139	18
Rapid (inflammatory)	26	4
Total	324	43

After Richards (61)

Fighting cancer by means of public education has resulted in shortening the period of delay between apparent onset and definitive treatment Toward the end of the last century Dietrich (12) in 1892 reported that in only 23 per cent of the cases in his series was the duration of symptoms less than six months Halsted (26) reported that 19 out of 76 operations for breast cancer were incomplete because of the magnitude of the growth and the hopelessness of the case ' He considered breast cancer a curable disease if operated upon properly and in time I cannot emphasize too strongly not losing a day

Reports from the United States and many other countries indicate that more patients are now being seen earlier in the course of their disease According to Harrington (30) of the Mayo Clinic during the period 1910 to 1914 only 32 6 per cent of the patients were operated upon within six months from apparent onset compared with 56 4 per cent operated upon within six months during the period 1935 to 1939 Lewis and Rienhoff (47) reporting the early Johns Hopkins Hospital breast cancer cases, found only 34 per cent of the patients seeking medical care within six months In New York Eggers, de Cholnoky and Jessup found only 36 6 per cent of their patients reported for treatment within the first six months In a careful review of London's Middlesex Hospital cases during the years 1936 to 1942 Bloom found that 65 per cent of the patients came for treatment within six months of their first symptom and 85 per cent came within 12 months.

The length of time from the observation of the first symptom to the time of definitive therapy was reported recently by Kaae (35) for the Radium Center of Copenhagen Table 61 shows that about one third (32

TABLE 61

Length of Delay Between Observation of First Symptom and Institution of Adequate Treatment in Carcinoma of the Breast in Women

Age at Observation of First Symptom	2 Weeks or Less	1 Month or Less	3 Months or Less	6 Months or Less	12 Months or Less	Total No. of Cases
years	%	%	%	%	%	
<40	18	31	40	64	84	45
40–49	16	32	49	67	82	100
50–59	16	34	57	71	80	120
60–69	19	31	51	67	90	118
≥70	22	31	47	64	82	74
All ages	18	32	52	67	81	475

After Kaae (35) 1948

per cent) of the patients came under treatment within one month, about one half (52 per cent) within three months, and about two thirds (67 per cent) within six months. There appeared to be no significant difference between the various age groups.

Nohrman (56) found that the average duration of symptoms before reporting to a doctor in patients attending the Radiumhemmet, was 8.8 months. Among 2,129 women with breast cancer in England, Hartnett (32) found that 56 per cent had symptoms for three months or more and 41 per cent had symptoms for six months or more, before consulting a doctor.

The duration of disease on admission was found by Haagensen and Stout to vary strikingly between private and ward patients. Private patients reported much earlier for treatment than did ward patients. During the first month after onset more than twice as many private patients (37.1 per cent) sought care than did ward patients (16.7 per cent). The reasons for this promptitude are not entirely clear but curiously enough they appeared to have no direct bearing on the end-results in this series.

The average duration of symptoms in several large series of cases is shown in table 62.

Warren and Witham (79), in an early study of metastatic patterns in 158 autopsied cases of breast cancer, noted the average delay from apparent onset to operation in 113 cases was ten months, and the average survival from operation was 36 months, for a total duration of the disease of 46 months. Lee and Tannenbaum (45), in a study of 363 cases treated by irradiation alone, found the duration of the disease to be 53 months. The average period from recurrence to death was 24 months.

TABLE 62

Author	Year	Duration of Disease
		months
Dahl-Iversen	1927	9.5
Weyl	1932	14.7
Nathanson and Welch	1936	12.0
Andreassen	1947	3.0

After Kaae (35) 1948

Duration of Disease and Prognosis

Perhaps it is well to consider the views which have been expressed regarding the duration of disease as an index of prognosis. Luff (50), in a study of over 1,500 cases for the British Medical Association, found that the longer the period of delay the poorer the prognosis. The four year survival rate for patients receiving treatment during the first month was twice as high as for patients receiving treatment after 12 months.

Hoopes and McGraw (34) noted that the five year survival rate decreased as the duration of the disease increased. This occurred in patients both with and without axillary metastases. MacDonald (52) found the most favorable survival rate in those patients who received surgical treatment within two months after discovering their tumors. Following this period a rapid deterioration in prognosis occurred. However, with a delay of one year or more the survival rate suddenly and rather surprisingly increased. Eggers, de Cholnoky and Jessup reported a five year survival rate of 76 per cent for patients operated upon within one month. The survival rate decreased rapidly with increasing duration of symptoms, falling to 20 per cent for a delay of one to two years. With further procrastination, however, the results improved, from 25 per cent for a lapse of two to three years to 41 per cent for an even longer interval. Nathanson and Welch found that patients with the shortest delay in treatment actually had the worst prognosis, whereas Lewis and Rienhoff (47), Kunath

(30) Hawkins (33) and Wevill (80) failed to find any significant difference whatsoever

Perhaps one explanation for the fact that the prognosis does not continue to deteriorate with the duration of the disease lies in the convincing concept that the more malignant and rapidly growing breast cancers receive earlier attention and treatment whereas, conversely the slow growing cancers receive later attention and treatment Korteweg (36) as early as 1880 pointed out with remarkable clinical discernment that breast cancer patients with the longest period of symptoms frequently showed the most favorable end results The survival of certain cases of late cancer with a low order of malignancy (or perhaps a high order of host resistance) was allowed to proceed during a prolonged period of delay by the laws of natural selection

Kaae found that operability depended upon the time which elapsed from the first symptom until definitive therapy was instituted All patients who reported for treatment within the first two weeks were technically operable (table 63) In those cases which came under treatment within two weeks 59 per cent were in Stage I 41 per cent were in Stage II and there were none considered inoperable With increasing duration of symptoms, the number of cases in Stage I became steadily less and there was a gradual increase in the number of cases classified as inoperable Kaae concluded that in the treatment of breast cancer 'it is of paramount importance for the result that adequate therapy is instituted as early as possible after the appearance of the first symptoms. This can only be achieved if the patients consult a physician as soon as they have noticed the first signs which might point to cancer of the breast, and if the diagnosis is established as soon as the case gets into the hands of the physician' What is gained in prognosis by the patient seeking medical care early must not be lost by the physician in procrastination or watchful waiting!

TABLE 63

Relation Between Delay and Operability and Between Delay and Stage of Disease

Delay	No. of Cases	All Cases: Technically operable	St. I	St. II	Inoperable
		%	%	%	%
2 Weeks or less	84	100	59	41	0
2 Weeks–1 month	60	94	53	41	6
1–3 months	92	89	43	46	11
3–12 months	140	77	31	46	23
Over 12 months	99	71	41	30	29
Total	475	85	44	41	15

Modified after Kaae (35) 1948

The relationship between duration of disease on admission and the five year clinical "cure" rate has been carefully recorded by Haagensen and Stout (23 25) In their 1915 to 1934 series of cases the "cure" rate fell, as expected with increasing duration of disease However the data in the 1935 to 1942 *series curiously failed to show this* correlation.

Bloom, in a critical study of duration of symptoms and prognosis found the survival rate to be uniform regardless of the delay However a slight difference in survival rate was noted when the histologic grade of malignancy was considered in relation to duration of disease and prognosis Time appeared to be of importance only for tumors of low grade malignancy The prognosis in 'highly malignant' breast cancers (grade III) appeared to be uninfluenced by the duration of the disease The survival rate was equally bad for these patients regardless of when they reported for treatment It was believed by Bloom that by the time such breast tumors were detected and diagnosed the dis-

per cent) of the patients came under treatment within one month, about one half (52 per cent) within three months, and about two thirds (67 per cent) within six months. There appeared to be no significant difference between the various age groups.

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Hoopes and McGraw (34) noted that the five year survival rate decreased as the duration of the disease increased. This occurred in patients both with and without axillary metastases. MacDonald (52) found the most favorable survival rate in those patients who received surgical treatment within two months after discovering their tumors. Following this period a rapid deterioration in prognosis occurred. However, with a delay of one year or more the survival rate suddenly and rather surprisingly increased. Eggers, de Cholnoky and Jessup reported a five year survival rate of 76 per cent for patients operated upon within one month. The survival rate decreased rapidly with increasing duration of symptoms, falling to 20 per cent for a delay of one to two years. With further procrastination, however, the results improved, from 25 per cent for a lapse of two to three years to 41 per cent for an even longer interval. Nathanson and Welch found that patients with the shortest delay in treatment actually had the worst prognosis, whereas Lewis and Rienhoff (17), Kunath

(30) Hawkins, (33) and Wevill (80) failed to find any significant difference whatsoever

Perhaps one explanation for the fact that the prognosis does not continue to deteriorate with the duration of the disease lies in the convincing concept that the more malignant and rapidly growing breast cancers receive earlier attention and treatment whereas, conversely the slow growing cancers receive later attention and treatment Korteweg (36), as early as 1880 pointed out with remarkable clinical discernment that breast cancer patients with the longest period of symptoms frequently showed the most favorable end results. The survival of certain cases of late cancer with a low order of malignancy (or perhaps a high order of host resistance) was allowed to proceed during a prolonged period of delay by the laws of natural selection

Kaae found that operability depended upon the time which elapsed from the first symptom until definitive therapy was instituted All patients who reported for treatment within the first two weeks were technically operable (table 63) In those cases which came under treatment within two weeks 59 per cent were in Stage I, 41 per cent were in Stage II and there were none considered inoperable. With increasing duration of symptoms, the number of cases in Stage I became steadily less and there was a gradual increase in the number of cases classified as inoperable Kaae concluded that in the treatment of breast cancer it is of paramount importance for the result that adequate therapy is instituted as early as possible after the appearance of the first symptoms. This can only be achieved if the patients consult a physician as soon as they have noticed the first signs which might point to cancer of the breast, and if the diagnosis is established as soon as the case gets into the hands of the physician ' What is gained in prognosis by the patient seeking medical care early must not be lost by the physician in procrastination or watchful waiting!

TABLE 63

Relation Between Delay and Operability and Between Delay and Stage of Disease

Delay	No of Cases	All Cases			
		Technically operable	St I	St. II	Inoperable
		%	%	%	%
2 Weeks or less	84	100	59	41	0
2 Weeks–1 month	69	94	53	41	6
1–3 months	92	80	43	46	11
3–12 months	140	77	31	46	23
Over 12 months	90	71	41	30	29
Total	475	85	44	41	15

Modified after Kaae (35) 1948

The relationship between duration of disease on admission and the five year clinical cure rate has been carefully recorded by Haagensen and Stout (23 25) In their 1915 to 1934 series of cases the 'cure' rate fell, as expected with increasing duration of disease However the data in the 1935 to 1942 series curiously failed to show this correlation

Bloom in a critical study of duration of symptoms and prognosis found the survival rate to be uniform regardless of the delay However a slight difference in survival rate was noted when the histologic grade of malignancy was considered in relation to duration of disease and prognosis. Time appeared to be of importance only for tumors of low grade malignancy The prognosis in "highly malignant ' breast cancers (grade III) appeared to be uninfluenced by the duration of the disease The survival rate was equally bad for these patients regardless of when they reported for treatment It was believed by Bloom that by the time such breast tumors were detected and diagnosed the dis-

TABLE 64

Delay from Apparent Onset to Treatment or Admission, by Stages of the Disease

Delay	Stage of Disease							
	I		II		III		IV	
	No	Per cent	No	Per cent	No	Per cent	No	Per cent
months								
1	71	(21.3)	47	(15.9)	15	(4.8)	2	(2.0)
1–2.9	70	(21.0)	63	(21.2)	38	(12.3)	5	(5.1)
3–5.9	57	(17.1)	42	(14.2)	43	(13.9)	15	(15.1)
6–11.9	49	(14.7)	67	(22.6)	67	(21.6)	14	(14.2)
12–23.9	40	(12.1)	34	(11.5)	62	(20.0)	12	(12.1)
24–35.9	21	(6.3)	17	(5.8)	26	(8.4)	16	(16.1)
36	25	(7.5)	26	(8.8)	59	(19.0)	35	(35.4)
Total	333	(100.0)	296	(100.0)	310	(100.0)	99	(100.0)
Median, in months (by interpolation)	4.0 ± 0.82		5.5 ± 0.63		11.5 ± 1.04		25.0 ± 1.73	

After Shimkin et al. (68) 1952

ease had already advanced well beyond the breast itself. Kreyberg and Christiansen (38) have studied the same problem, considering the grades of breast tumors, and have supported the conclusions of Bloom. As noted by Kreyberg (37), however, these conclusions may hold good for groups of cases, but in each individual case independent behavior based upon many factors makes prognosis much less predictable.

The statistical analysis of Shimkin and his colleagues (68) in 1,038 cases of breast cancer is shown in table 64. From this study there appears to be a significant difference in the several stages of disease which are closely related to the duration of delay. The median period of delay for Stage I and Stage II was four months and 5.5 months respectively. Whereas the median period of delay for Stage III was 11.5 months and for Stage IV it was 25.0 months. These differences are striking and statistically highly significant.

In a critical computation of the mean survival of women with cancer of the breast, from apparent onset to five years after treatment, according to delay, Shimkin et al. have shown that the average patient lives for 45 months if there has been less than one month of delay, whereas the average patient lives for 66 if there has been a delay of 36 months. These data, of course, must not be distorted to suppose that delay is desirable. Such is certainly not the case. Presentation of survival data which takes into consideration duration of delay and stage of disease is at the mercy of biological selection. Cases of rapidly growing and highly fatal malignancies fall into one end of the survival scale whereas slow growing tumors fall into the other end of the scale. The tremendous influence of the biologic properties of tumor activity and host resistance is clearly demonstrated.

The results of most analyses indicate that delay has a definite influence in determining the clinical stage of the disease, its operability and its prognosis. It is occasionally true, despite the apparent paradox, that even a long delay in some cases may not adversely alter the stage of the disease or the prospects

for survival Conversely the least delay possible does not necessarily exclude the hazard of early metastases Thus, the prognosis may be grave in a patient with a short history and an active cancer, or the prognosis may be good in a patient with a long history and an indolent cancer All things being equal however, the longer a breast tumor is present the greater the opportunity for growth metastatic spread and an unfavorable end-result

Many clinical investigators have correlated the time lag between the first sign or symptom of breast cancer and the onset of definitive treatment with dissemination and prognosis. Since most tumors begin as a local proliferation and subsequently grow and spread, it has generally been accepted that the shorter the delay the better the result Regardless of our increasing diagnostic acumen in this insidious and silent disease we are seriously handicapped by inadequate criteria with which to make a truly timely diagnosis. As aptly stated by Kreyberg our surgical failures are the result of delay in the sense that an important number of patients have already developed metastases, beyond therapeutic control at the moment of the earliest possible diagnosis" All of us must become increasingly alert to the danger of breast cancer on less and less clinical evidence

Significance of Tumor Size in the Prognosis of Breast Cancer

It is generally conceded that the size of the primary tumor at the time of diagnosis or operation is a very important factor in the prognosis of a patient with cancer of the breast The smaller the size the better the prognosis is considered virtually a self evident truth However the validity of this assumption is not entirely without question

Dahl Iversen (7) notes that patients with small breast cancers are free of metastases or recurrences in 83 per cent of the cases three years after operation whereas patients with larger tumors are free of recurrence in only 13 per cent after a similar postoperative period Eggers, de Cholnoky and Jessup report a five year "arrest" of 72.5 per cent if the primary breast tumor is two cm or less, a 24 per cent five year "arrest" if the tumor is between two and six cm in size and only a 15.5 per cent "arrest" for larger tumors. Haagensen and Stout noted a five year clinical "cure" of 62.2 per cent if the breast tumor was less than three cm, and only a 10 8 per cent five year clinical "cure" if the tumor size had reach six cm or more "The data indicate as might be expected that the prognosis becomes worse as the size of the tumor increases." In a later report, Haagensen (22) noted a mean diameter of 4.8 cm in the clinical tumor size of a large series of patients with primary breast cancer The incidence of axillary metastases in this group was 70 per cent In contrast with this, a highly selected group of patients were studied in whom the clinical tumor size measured less than 1 5 cm The incidence of axillary metastases in this group was only 11 per cent Since prognosis and ultimate survival is closely related to the incidence of axillary metastases, its correlated dependence upon tumor size grade of malignancy and duration of disease is obvious

Stewart (73) has studied the surgical pathological material at the Memorial Hospital in New York. Based upon tumor size recorded by the pathologist (table 65) Stewart believes that "in infiltrating mammary carcinoma the most significant data for purposes of group prognosis, but not individual cases are the largest diameter of the primary tumor and the condition of the axillary nodes"

Eggers, de Cholnoky and Jessup found that the percentage of axillary metastases was in direct relation to the size of the tu

TABLE 65

Table of Five-Year Clinical Cure Rates in Cancer of the Female Breast According to Size of the Primary Tumor (Pathologist's Dimensions, Memorial Hospital)

Based on 1355 primary operable cases treated by radical mastectomy with determinate end results (1935–42 admissions)

Largest Dimension of Primary Tumor	Cases and Percentage	Breast Only Involved	Breast and Axilla
Less than 2 cm., number of cases	201	121	80
5 year clinical cure rate, per cent	74.1	87.6	53.8
2.0 to 2.9 cm., number of cases	396	185	211
5 year clinical cure rate, per cent	60.2	74.6	47.9
3.0 to 3.9 cm., number of cases	318	119	199
5 year clinical cure rate, per cent	47.8	68.9	35.2
4.0 to 4.9 cm., number of cases	183	65	118
5 year clinical cure rate, per cent	41.5	60.0	31.4
5.0 cm. and over, number of cases	257	57	200
5 year clinical cure rate, per cent	33.5	*75.4	21.5

* This figure may appear peculiar. It is somewhat elevated, because in the 5.0 cm. and over group there are included some of the bulky medullary carcinomas with lymphoid stroma which carry a better average prognosis.

No further proof is needed to show the importance of early recognition of mammary cancer.

After Stewart (73) 1950

mor. There is progressive axillary involvement with increasing size of the tumor (table 66).

Bloom, in a study of 350 cases, found the following five year survivals:

	%
Primary breast tumor less than one inch	59
Primary breast tumor one to 2 inches	45
Primary breast tumor two inches or more	32

However, as noted by Geschickter, "the size of the tumor is a reliable index of prognosis only if the pathological type is taken into consideration." Bloom, an advocate of the merits of histologic grading, believes that allowance must be made for tumor grade as well as size in determining prognosis. These three factors, grade, size and prognosis, are considered in the figures in table 67.

It is evident, from this study at least, that tumor size alone appears to be of no prognostic significance in breast cancer with either a high or low degree or grade of malignancy. In tumors which are grade I, the prognosis is uniformly good regardless of size and, in tumors which are grade III, the prognosis is poor regardless of size. However, only in grade II does tumor size bear a direct relationship to prognosis—"the larger the tumor the greater the likelihood of spread having taken place."

On the other hand, Kunath states that "an analysis of this point failed to reveal that a larger tumor carries any more serious prognosis than does a smaller one." Hoopes and McGraw also concluded that there was no correlation between postoperative survival and initial tumor size.

Considering the importance of determining the significance of tumor size in the prognosis of breast cancer, Kreyberg and Christiansen have critically analyzed 974 cases of breast cancer. The fate of their patients was carefully followed for from ten to 20 years. Only 56 tumors (5.7 per cent) were small (the size of a hazel nut or smaller), and, of this group, 66 per cent survived five years or longer. If grade I tumors were eliminated, only one third of the patients then survived

Considering only the very smallest tumors in the 'small' group (the size of a pea or bean) this study revealed a ten year survival of 50 per cent Kreyberg and Christiansen conclude that size alone is not decisive and that small tumors in clinical Stage I or Stage II do not indicate a more favorable prognosis than one might expect for similarly classified cases of breast cancer of larger size

Thus, the prognosis based upon tumor size or duration of disease certainly cannot be regarded as an infallible index of survival The matter must be more complex and dependent upon many factors such as degree of malignancy growth rate and host resistance Although our tendency is to 'celebrate our therapeutic triumphs when the degree of malignancy of a tumor is small" yet it is well to recognize the lack of our knowledge regarding the still unpenetrated reasons for these more fortunate results.

Significance of Tumor Site

The location of the primary tumor within the breast has been regarded by some with special interest in predicting prognosis Lane-Claypon in a detailed analysis of the frequency of site in 6 464 collected cases of breast cancer found the upper and outer quadrant to be the anatomical area most commonly affected This frequency is generally recognized in almost all series (Fitts and Donald (16) 58 per cent, Deaton Postlewait and Bradshaw (10) 59 per cent) and various reasons have been given to account for this predilection of position It has been pointed out that the axillary tail extending upward and outward may be especially exposed to various forms of injury incident to household chores or even brassiere straps and wire bands. The anatomic and functional relationship between the body of the breast and its axillary prolongation may be imperfect resulting in secretory stasis and irritation. Nicholson and Grady (55) noted that breast cancer occurred in the upper half of the breast in 80 per cent of their series Pre-existing benign breast disease caused by poor breast support was regarded as an important etiologic factor predisposing to the upper half of the breast Deaton and Bradshaw (9) suggest that breast cancer arising in aberrant breast tissue may be difficult to diagnose particularly when the aberrant tissue and normal tissue are contiguous. The most frequent location of aberrant breast tissue is in the upper and outer quadrant of the breast It occurs in from one to seven per cent of the normal population Finally it must be recognized that the major bulk of the breast tissue actually occurs in the upper and outer quadrant, thus rendering it proportionately more liable to malignancy

TABLE 66

Relation of Tumor Size to Axillary Metastases

	Tumor Size (Cm.)					
	0 5	1	2	3	4	5
No of cases	5	12	23	50	35	24
No with axillary metastases	1	3	7	30	24	20
Per cent	20	25	30 4	60	68 5	83 3

After Eggers deCholnoky and Jessup (14)

TABLE 67

Grade	Tumor Size	Cases	Five Year Survival	
			No.	Per cent
I	1 or less	64	49	77
	More than 1	42	33	79
II	1 or less	68	40	59
	More than 1	81	27	33
III	1 or less	40	12	30
	More than 1	55	16	29

After Bloom (1950)

TABLE 68

Incidence of Breast Carcinoma According to Site (Middlesex Hospital)

Site	Present Series (1936 to 1942), 385 Cases		Campiche & Barlow, 1905 (1747 to 1903), 1010 Cases	Beckton, 1909 (1904 to 1909), 230 Cases	Truscott, 1947 (1926 to 1938) 836 Cases
	Cases	Per cent			
			%	%	%
Upper outer	177	46	45	46	46
Upper inner	75	19	17	20	20
Central	35	9	20	15	13
Lower outer	54	14	12	13	12
Lower inner	19	5	6	5	5
Axillary tail	7	2	—	1	4
Diffuse or whole breast	18	5	—	—	—
Total	385	100	100	100	100

After Bloom (2) 1950

In a survey of 1,000 cases of breast cancer, Geschickter (18) found that approximately 60 per cent of the tumors occurred in the outer hemisphere, 18 per cent in the inner hemisphere and 22 per cent in the central area. The most common site was the upper and outer quadrant which gave rise to 44 per cent of the tumors.

The incidence of breast cancer according to site has been shown to have remained rather constant over a long period of time (table 68) despite changes in feminine fashion and women's domestic chores. According to Bloom, the frequency of site noted at the Middlesex Hospital in London differs in no way *from similar studies* of a yesteryear. The overwhelming predominance of upper and outer quadrant tumors (44 per cent) is a most striking feature of Haagensen and Stout's most recent survey.

The relationship between site of tumor and prognosis has been given serious consideration by many investigators. Some years ago Sampson Handley (28) pointed out that the prognosis of lesions located in the inner half of the breast was much worse than those located in the outer half of the breast. Handley attributed this to the greater risk of metastases to the mediastinum and lung along the crucial avenue of the internal mammary lymphatics (see Chapter II).

Bartlett (1) has demonstrated in a rather striking manner the importance of tumor site on the end-results of surgical treatment (table 69).

TABLE 69

Hemisphere	Without Axillary Nodes, 5 Yr Survival	With Axillary Nodes, 5 Yr Survival
	%	%
Outer	77	29
Inner	17	4

After Bartlett (1933)

Richards believes that the location of the tumor deserves much more attention than it receives, and site should be given "serious consideration in deciding upon the procedure to be followed." Hawkins found the five year survival rate for breast cancer of the inner hemisphere to be 52.1 per cent as compared to 61.6 per cent for the outer hemisphere. Breast cancer of the lower inner quadrant, in the experience of Haagensen and Stout

had the highest local recurrence rate and the lowest "cure rate throughout several carefully reported series.

According to Nohrman the prognosis is significantly better for lateral tumors only in clinical Stage I of the disease. No difference in prognosis with a difference in tumor site could be demonstrated in Stage II The data of Smithers et al., corrected for expectation of life and for stage distribution within each group revealed a slightly lower survival rate for inner quadrant lesions but the figures were not considered statistically significant

Some authors regard the upper and outer quadrant of the breast and others the lower and inner quadrant of the breast, as being the site of poorest prognosis In one case the proximity to the axillary nodes and in the other the relation to the internal mammary nodes are held responsible A similar inconsistent but justifiable opinion has been expressed for the nipple region or central area of the breast In the anatomy of the lymphatic system, both Rouvier (62) and Sappey (64) have clearly demonstrated the importance of the subareolar plexus. Grant, Tabah and Adair (19) have shown experimentally the constant and characteristic pattern of lymph flow in the breast which occurs in a centripetal direction toward the areola Drainage of the parenchyma of the breast occurs centrally to the critical subareolar plexus before outflow to the regional nodes occurs (see Chapter II)

Lane-Claypon in her comprehensive survey concluded that infection of the axillary glands occurs most readily from growths situated centrally and outwardly that while growths situated inwardly' do not cause early involvement of the glands of the axilla they may be more dangerous than growths in other sites, owing to the easy access to the thorax. In a later and more extensive analysis of results Lane-Claypon could find no

TABLE 70

Site Grade and Prognosis

Grade	Outer Hemisphere			Inner Hemisphere		
	Cases	5 year survivors		Cases	5 year survivors	
		No.	Per cent		No.	Per cent
I	76	65	86	29	21	72
II	100	47	47	37	15	41
III	67	18	27	28	8	29

After Bloom (2) 1950

evidence that prognosis varied according to tumor site Breast cancer cases classified separately by clinical stages again showed no indication that prognosis differed in the various quadrants of the breast Similar conclusions have been expressed by Truscott (75) and Hartnett (32) Bloom considered it "possible that growths situated in the sternal quadrants and in the nipple area carry a slightly worse prognosis than do those in the outer regions. As noted by Handley and Thackray (27), these are the patients who are most likely to have internal mammary node metastases

By applying the principle of histologic grading to the problem of tumor site and prognosis, Bloom found (table 70) that site was of some significance only in grade I breast carcinomas He concluded that the tumor site in cancer of the breast exerted no striking effect on end results. Thus, prognosis appears to be perpetually dependent upon many subtle properties, which when taken together may exert a powerful influence on survival.

Factors of Prognosis in Recurrent Breast Cancer

In a unique study of two groups of patients who were (1) first seen for recurrent breast cancer and (2) first treated by radical mastectomy and who subsequently developed recurrent or metastatic disease

Shimkin, Lucia, Low-Beer and Bell (67) investigated the problem of prognosis both before and after recurrence. Although the work of the Soviet investigators Shabad and Golbert (65), and the Americans, Pack (57), Slaughter (70) and others suggest that multicentric primary breast cancer may occur not infrequently, it is fair to assume that late recurrences and metastases almost always represent dissemination from the primary focus

The data of Shimkin's study concerning 261 recurrent cases of breast cancer were compared with and combined with data concerning 372 cases of primary breast cancer who developed subsequent recurrences and metastases It was demonstrated that the length of life in the latter cases is dependent upon 1) the stage of the disease at the initial operation (fig. 123), and 2) upon the type of first metastasis or recurrence (fig 124) noted clinically (local, osseous or general)

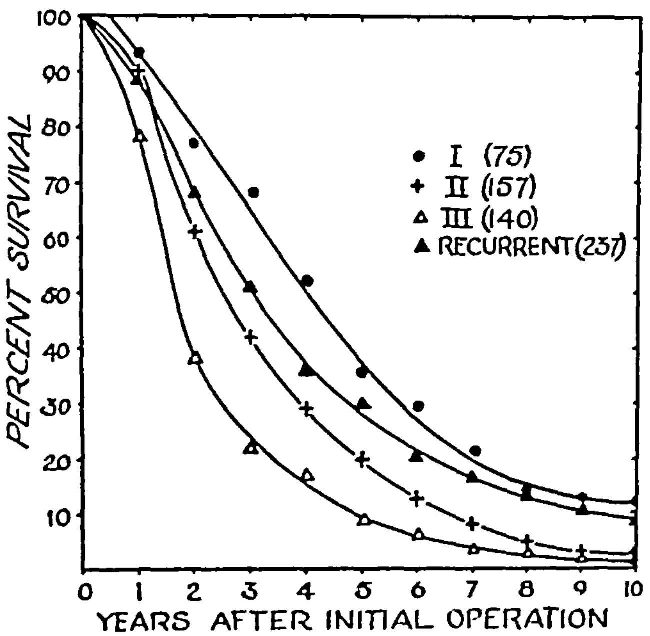

FIG. 123 Survival of female patients with breast cancer treated by radical mastectomy These patients subsequently developed metastases or recurrences and died of the disease Graphically represented according to the stage of the disease at the initial operation, against years of survival after initial operation Included is the survival of 237 patients who were first observed with recurrent or metastatic disease and who subsequently died of breast cancer

The five year postoperative survival rate of patients who eventually died of breast cancer was 36 per cent for Stage I patients, 20 per cent for Stage II patients and nine per cent for Stage III patients

There appeared to be no relationship between years of survival and age of the patient at the time of initial operation This study did not reveal a significantly greater proportion of rapidly growing breast tumors among young women The clinical stage of the disease appeared to be unrelated to the patient's age

The time following operation at which point recurrences or metastases might become manifest was influenced by the stage of the disease at the time of operation Survival following the clinical appearance of recurrences or metastases bears a very close relationship to the length of life from the initial operation to the onset of secondary disease The length of life after recurrence was influenced to a major degree by the type of recurrence or metastases Following local recurrence the survival period was longest (28 months), following osseous metastases (24 months), and after generalized metastases the survival period was shortest (10 months)

Summary and Conclusions

The clinical problems of prognosis have been intensively studied by many investigators over a period of many years A wealth of clinical and statistical information has been accumulated, but there still remains no unanimity of opinion regarding its validity or significance as an index of prognosis for the individual patient with breast cancer Each factor of prognosis is merely a straw in a wistful wind

From scattered reports throughout the literature Morton and Morton (63) have collected a series of unique cases (table 49) indicating the inconstant natural history or clinical behavior of breast cancer In some cases cancer may disappear spontaneously while in others it may grow only in periodic cycles. Observed not infrequently is the phenomenon of delayed recurrence with local recrudescence within the area of operation many years after radical mastectomy At times tumor cells appear almost guileless by microscopic examination, lying latent and deceptively dormant within the natural defenses of the body After a variable period of presumed quiescence cancer cells often *regain their flagging virulence and take on* characteristics of rapid growth and extra ordinary malignancy Thus, prognosis is unpredictable and cancer today gives no sure measure of cure tomorrow

Tumors are known to vary greatly in their growth rate and in their tendency to metastasize early The measure of earliness in time for the purpose of prognosis lies not alone in minutes or months but in malig nancy and metastasis The slender thread *of time delayed therefore may mean those* patients who lose a day lose a life ' Prog nosis is primarily a balance between the malignant potential of the tumor cell and the biologic resistance of the host Radical mastectomy or even more extensive radical surgery promptly performed will be life saving only in those patients *in whom the* tumor has not yet spread beyond the con fines of the field of operation Thus the prog nostic significance and importance of axillary metastases (both presence and extent) or metastases to other accessible regional nodes are obvious However such factors as dura tion of disease size site or *grade of tumor* and the age of the patient are in themselves uncertain prophets of *prognosis*.

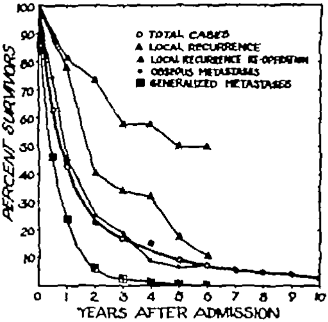

Fig 124 Survival of 261 patients with recur rent breast cancer against years after admission to the University of California Hospital by type of recurrence at the time of admission Local re currence 60 cases osseous metastases 31 cases and generalized metastases 143 cases

Clinical attempts to determine the degree *of cancer malignancy by evaluating the* relevant factors of prognosis have been numerically expressed by Leo and Stuben bord (44) and Richards, as the Clinical Index of Malignancy " Such an assessment may be desirable to indicate tumor activity and less likely host resistance in a large group of patients, but the treatment policy in the individual patient can hardly be based upon an arbitrary numerical digit.

With true humility we must confess that *despite* prompt and adequate treatment we do not know precisely which individual pa tient will be favored by fortune and granted a long survival Certainly the cardinal *con* cept of early diagnosis and early *treatment* well done cannot help but contribute toward this *hope and expectation*

The most important measurable factor in the prognosis of breast cancer is the presence and the extent of axillary metastases at the

time the patient is first treated Age, duration of disease, size, site and grade of tumor are all factors of secondary significance Trauma, surgical and radiotherapeutic treatment, the effects of biopsy and delayed operation, and pregnancy and lactation have been separately discussed elsewhere The questionable influence of ovarian stromal hyperplasia on survival in both treated and untreated cases of breast cancer has been found by Sommers, Teloh and Goldman (72) to be negligible

While some of these factors may be related to the alertness and understanding of the patient and the diligence and initiative of the physician, as stated by Smithers et al, prognosis "is largely dependent on the rate of growth and tendency to dissemination of the tumour"

In the dilemma of prognosis, currents and cross currents of biologic behavior flow beneath the surface of unpredictable clinical speculation The measure of these forces and their influence on survival cannot as yet be calculated with certainty

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CHAPTER XV

Radiotherapy of Breast Cancer

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Views concerning the role of radiotherapy in the treatment of breast cancer are so completely at odds that it is evident that gross misconceptions must exist as to the effect of radiation on this disease Taylor (10) has written that he has seen no evidence that radiation has increased survival or diminished the incidence of recurrences following surgery McWhirter (6 7) has questioned the usefulness of axillary dissection and relying on simple mastectomy and radiotherapy he has apparently equalled the survival rates reported for radical mastectomy In order to offer a rational basis for incorporating radiotherapy in a treatment policy for breast cancer, it is necessary to attempt some reconciliation between these divergent views

That radiotherapy has some effect upon breast cancer is readily demonstrable in any series of patients having proved lesions accessible for observation Bulky lesions diminish in size ulcerated lesions are observed to heal metastases in skin or lymph nodes disappear clinically and bone at the site of osteolytic lesions may be reconstituted All lesions of breast cancer do not show an equal response, and regression of a tumor mass may not be complete or permanent Even with satisfactory clinical regression or disappearance of such lesions, cancer in the treated region may not be eliminated Histologic examinations of breast specimens months or years after radiotherapy may demonstrate persistence of occult cancer cells (2) Whether or not complete eradication is attained the repressant effect on breast cancer is real The importance of this effect depends upon the number of patients who are eligible for this form of treatment alone or combined with surgery

Radical mastectomy is generally regarded as the form of treatment offering the best chance for cure of breast cancer but for a considerable number of patients it is not applicable at the time of diagnosis Accepting the published experience of Haagensen (2) and Taylor (10) 30 out of any 100 consecutive unselected patients may be expected to be inoperable when first seen (see Chapter XI) New evidence of early metastases to the internal mammary and supraclavicular lymph nodes further limits the number of patients eligible for surgery (see Chapter II) Of those subjected to radical mastectomy about one half can be expected to be free of clinical evidence of disease for five years (10) This means that approximately two thirds of any 100 consecutive, unselected patients will be either unsuitable for surgical treatment or will not be cured by surgery For these patients radiotherapy becomes the chief recourse and from the very number involved, radiation

assumes a major role in the management of breast cancer

Under certain circumstances, radiotherapy may be employed as palliation, as prophylaxis, or as definitive treatment for apparently curable disease

Indications for radiotherapy are clear in some instances of inoperable breast cancer, or recurrent or persistent disease in the operated site following surgery, and for metastatic lesions, particularly when these are responsible for the symptoms which contribute to the patient's discomfort Treatment in these categories is termed palliation because it is evident that the chance for cure is extremely remote Palliation is an excellent term meaning to mask disease, and, in this sense, it is descriptive of much of medical practice Unfortunately, the word has come to have a connotation of futility and the method is applied as either a placebo or an act of desperation These patients may live for many months or even years, and effective control of local lesions is just as important to them as if cure were still a possibility

Radiotherapy has been widely used in combination with radical mastectomy in the hope of improving the results obtained by surgery alone The logic of this application is that if visible disease can be controlled by radiation, then the appearance of metastases might be prevented or delayed by treating cancer cells either before they metastasize, or before they grow to recognizable proportions It has been used preoperatively to diminish the size of bulky lesions and thus simplify the technical procedure of removal It has also been used in the hope of injuring tumor cells by radiation preoperatively and thus diminishing the likelihood of metastases It has been used postoperatively in the hope of diminishing recurrences in the operative site, and to control or eliminate possible metastases in the supraclavicular or internal mammary regions which are not readily accessible to surgical removal Postoperative radiation is undertaken when it is considered probable that cancer cells are present in the operative site or in the immediately adjacent lymphatic drainage areas Since the presence of cancer is not known with certainty, the treatment is termed prophylactic In some series, preoperative and postoperative radiotherapy are combined with radical mastectomy (8)

The third way in which radiotherapy is used is neither for palliation nor prophylaxis but for the definitive control of the disease The controversial treatment policy of McWhirter (6, 7) utilizes radiation in this fashion The primary lesion is removed by simple mastectomy and any residual disease on the chest wall together with metastases in axilla, supraclavicular region or internal mammary region, is treated solely by radiation The rationale of this treatment policy should be understood because the results now available appear to be equal to those produced by radical mastectomy

Reviewing the results of treatment of breast cancer by radical mastectomy at the Royal Infirmary at Edinburgh, McWhirter noted that when there were no axillary metastases, a five year survival rate of approximately 70 per cent was being achieved When metastases had occurred to axillary lymph nodes, the five year survival rate dropped to approximately 30 per cent despite treatment by radical mastectomy with axillary dissection which had been developed to cope with metastases to the axilla He reasoned that if disease were confined to the breast, then simple mastectomy without axillary dissection should achieve cure If metastases were present in the axilla, axillary dissection was not conspicuously effective in achieving cure, and at least as much might be accomplished by radiotherapy to this region With the concurrence of the surgical staff at the Royal Infirmary, a program was

set up in which the *basic treatment policy* for breast cancer would be simple mastectomy followed by a rigidly prescribed and executed course of radiotherapy

The results of these three major treatment policies are shown in table 71

An absolute survival rate is based upon the total number of patients seen whether treated or untreated and the total number of these who are living with or without known disease. For purposes of comparing results in different centers, this method is preferable to a relative survival rate which is based upon the total number of patients subjected to operation and the total number of these who are living with or without known disease The relative survival rate would depend upon the strictness with which patients were selected for operation and this is a factor which could vary from one center to another The absolute survival rate removes this element of selection although there still may be some variations For example Haagensen (2) and McWhirter (6) deal only with female patients who had received no previous treatment whereas Nohrman (8) counts all admissions to hospital both male and female, apparently without reference to previous treatment An absolute survival rate is subject to certain hidden elements of selection when for instance geographic social or economic conditions tend to direct operable patients to one institution and advanced and inoperable cases to another The reputation of an institution can influence the type of patient referred for treatment

Radiotherapy may be undertaken for three quite different purposes—palliation prophylaxis or definitive treatment The possible benefit to the patient will vary in nature and degree and may not always be measured simply in terms of survival The problem of how to measure the benefit derived from any form of treatment for patients with breast cancer is largely responsible for the sharply differing views as to the effectiveness of radiation.

TABLE 71

Effect of Treatment on Survival of Patients with Cancer of the Breast

Treatment Policy	Absolute Survival Rate	
	5 years	10 years
Radical mastectomy Haagenson (2) Presbyterian Hospital New York	47 2% 315 of 668 pts 1935–1942	No available data
Radical mastectomy with pre and post operative radiotherapy Nohrman (8) Radiumhemmet Stockholm	40 1% 417 of 1,042 pts 1936–1941	23 4% 36 of 154 pts 1936–1937
Simple mastectomy with radiotherapy McWhirter (7) Royal Infirmary Edinburgh	42 0% 786 of 1,882 pts 1941–1947	25 0% 122 of 480 pts 1941–1942

There is a tremendous variation in the natural duration of the disease as seen either in untreated patients, or in treated patients who are not cured No author reporting survival rates intentionally implies that all surviving patients are living solely as the result of treatment Available evidence concerning untreated breast cancer (9) is that approximately 20 per cent of such patients will survive five years or more (see Chapter XIV) In a treated series, an absolute five year survival rate of approximately 40 per cent may be expected and the difference between these two figures sometimes is taken as an index of the effect of treatment The figures are not comparable however for the survival of untreated patients is measured from the time of onset as related by the patient whereas for the treated

series, duration is measured from the time of diagnosis or treatment For purposes of comparison, this places the treated group at a disadvantage The comparison of survival rates is not valid for the further reason that the two groups of patients are not comparable The patients who comprise untreated groups are apt to be those who were untreated because of advanced disease The five year survival of an unselected and untreated group containing both operable and inoperable stages of the disease would be expected to differ from the five year survival of an operable but untreated group, or an inoperable and untreated group It is evident therefore, that a firm baseline is lacking against which to measure any increase of survival for a patient with breast cancer treated by any method

For the group of patients with known and evident disease at the time of treatment, response of local disease can be determined at an early date If this is satisfactory, there may be conjecture as to whether survival is altered, but failure to establish this does not detract from the immediate local benefit

When radiotherapy is used in conjunction with radical mastectomy, the purpose is to prevent local recurrence and to prolong survival time These are quite different effects One might be achieved without the other, and, together or singly, success is difficult to prove

If radical mastectomy alone is the method of treatment, the possible causes of failure are: 1) extension of the disease beyond the resectable tissues before operation, 2) dissemination of metastases by manipulation during the surgical procedure, 3) or persistence of disease due to technical inadequacy of the procedure employed If there has been distant spread of disease either before surgery or at the time of operation, then no improvement in survival can be expected by the addition of radiotherapy to the operated site or to the immediately adjacent lymphatic drainage areas

The circumstances under which radiotherapy might conceivably improve results of radical mastectomy are these

1. Given pre-operatively, radiation might so injure tumor cells that persistent tumor in the operative site or metastases disseminated during operation could not grow

2 If cancer persists only locally in the operated site, it is possible that the addition of postoperative radiotherapy might prevent local recurrence and eventual distant metastases

3 If the disease had spread just beyond the limits of resectability, to the supraclavicular region or to the internal mammary lymph nodes, then, conceivably, postoperative radiation to these regions might prevent or delay further spread of metastases

Although radiation might be carried out with these reasoned objectives, the recognition of either success or failure is difficult or impossible It is not surprising that the incidence of local recurrence seems unaltered The comparison is apt to be between favorable instances treated by radical mastectomy alone and patients who, because of a high likelihood of recurrence, received combined treatment Failure is documented by recurrence but delay or prevention of recurrence cannot be recognized The chance for cure is known to be lost when distant metastases are recognized, but it cannot be determined whether these occurred before or after treatment As long as the patient who has received combined treatment continues free of disease, the success is apt to be considered primarily surgical because the prophylactic irradiation was not given with the certain knowledge that disease persisted When distant metastases become evident following treatment, it cannot be determined whether these were present and unrecognized before treatment or whether they represent a true

failure of treatment to control disease while it was still localized

It is necessary to account for the similarity of the survival rates for series treated by radical mastectomy and those treated by simple mastectomy plus radiotherapy It must be assumed that the patients of each group are comparable and there would be equal proportions in these three categories a) patients with disseminated disease who would not be cured by either method b) patients with disease confined strictly to the breast who should have an equal chance for cure by either simple or radical mastectomy, c) patients with metastases limited to the axilla in whom any difference in effectiveness of radiation and dissection may be crucial to survival Since there is little difference in the survival rates for the two treatment policies, one of the following explanations must hold

1 Radiation and surgery are equally effective in controlling axillary metastases

2 The number of patients who have metastases limited to the axilla is so small that the outcome of treatment has little influence on the overall survival rate.

The latter view is supported by increasingly strict criteria of operability that have been recommended as a result of recognition of metastases to the internal mammary and supraclavicular regions (5)

Biologic Effects of Radiation

Radiation reacts with matter by ionization and excitation of atoms These processes result in chemical reactions and in physical alterations in molecular structures. When radiation reacts with living tissue it is almost impossible to recognize the direct effects, but these are reflected in changes in function Such changes are the inhibition of mitoses, the production of mutations, the inhibition of enzyme systems disturbance of electrolyte concentration and altered permeability of cell membranes. Even these intracellular changes are not necessarily direct effects of irradiation for the life of the cell may be jeopardized by interfering with a single enzyme system In a composite tissue where cells of many types are interdependent for survival injury to the vital processes of one or more small groups of cells may produce secondary changes throughout the tissue which will not be directly or specifically, the effect of radiation Grossly, the first response to radiation is inflammation of normal tissue or shrinkage of tumor masses and the late effects are atrophy and degeneration sometimes appearing after a long latent period The immediate histologic effects may be cell injury or death hyperemia, interstitial edema and cellular infiltration The late microscopic effect may be permanent changes in the vascular bed fibrosis and cellular degeneration and atrophy Neither the gross nor the microscopic findings are specific for radiation effect, and they yield no information as to the actual mechanism by which radiation initiated the damage to tissue

The usefulness of radiotherapy in the treatment of cancer lies in the varying sensitivity shown by different tissues either normal or neoplastic As a general rule, the more rapidly growing tissues are more sensitive and, since neoplastic tissue is characterized by more rapid growth than normal tissues, it may be expected to be more sensitive to radiation The problem of radiotherapy is to utilize this difference by observing the tolerance of normal tissues and taking full advantage of the relatively greater radiosensitivity of tumor cells.

Radiation is never considered beneficial to either normal or tumor tissue, and in this sense, it may always be considered injurious. The effect of radiation will vary with dose from no known effect through acceptable reactions to severe injury producing a com

plication of treatment. A normal tissue is said to tolerate radiation if it sustains the effect and heals. Tolerance is the maximum reaction that normal tissue can sustain and still permanently heal. The tolerance dose for a given tissue is the amount of radiation which produces such a reaction.

The principles that govern the tolerance of living tissues to radiation are comparable to those that govern the severity of thermal burns. In both cases the injury will be proportionate to the amount of radiation or heat. For similar intensities of radiation or heat, the severity of the injury will depend upon the area exposed and the length of time of the exposure. In prescribing the dose of radiation which will have a predictable effect upon normal tissues, it is necessary to remember that this cannot be described without taking into account the amount of radiation, the length of time over which the radiation is to be delivered, and the area of skin or volume of tissue which will be subjected to radiation. These considerations are particularly important in irradiation of the intact breast. If an amount of radiation which is just within the tolerance of a small breast is given to a large breast and in the same period of time, a very severe reaction can be expected.

A tumor is said to be radiosensitive if it undergoes reduction in size as a result of radiation. Radiosensitivity is not an absolute characteristic because there are all degrees of response. Rapid and complete disappearance of grossly evident tumor may be caused by an amount of radiation having no apparent effect on normal tissue. There may be no apparent influence on tumor produced by amounts of radiation large enough to destroy adjacent normal tissues.

The desirable goal of radiation would be to produce a cancerocidal effect, i.e., to kill every tumor cell without destroying surrounding normal tissue. This is not a practical goal and the use of the term cancerocidal effect, or cancerocidal dose, might well be abandoned for these reasons:

1. In vitro experiments with haploid yeast cells indicate that for large numbers of cells, a few may be killed by very small amounts of irradiation and a few will remain apparently viable in spite of extremely large doses of radiation. It might be expected that rarely, if ever, can every cancer cell be destroyed by radiation without excessive damage to adjacent normal tissues.

2. If a cancerocidal effect were produced, it would be impossible to confirm it. The disappearance of every tumor cell from the treated site could never be proved even by serial sections of large masses of tissue. Should such a study ever be undertaken, persistent tumor cells may well be recognized but this would not rule out a cancerocidal effect since no time limit is established within which the effect of radiation must occur. In normal tissues we are accustomed to see the late degenerative effects first appear after many years. A similar delayed effect may also result in the death of cancer cells which have persisted, apparently viable, for a long time after irradiation.

When a tumor manifests radiosensitivity, diminution in bulk or size may occur by a variety of mechanisms. a) Some cancer cells or even the bulk of cancer tissue may be killed as a direct effect of radiation. b) Remaining tumor cells may have a diminished potentiality for growth. c) Remaining tumor cells may be so damaged that they are unable to reproduce and in the course of time die off. d) It is believed that the normal tissues in the tumor bed play an important role in the completion of destruction of tumor cells damaged by radiation. This is a cleaning up action, comparable to the reaction of normal tissue to infection. If the tumor bed has been over-irradiated by what has been termed a supralethal dose, it is con-

sidered that the direct effect of irradiation alone may be inadequate to destroy tumor and that growth will recur even in the midst of necrosis of normal tissue c) It has long been held that dense fibrous tissue reaction and sclerosing effect of radiation upon lymphatics prevent the growth and spread of cancer even though apparently viable cells persist These mechanisms are the demonstrated effects of radiation and singly or in combination exert a control on the growth and spread of cancer

On the basis of these considerations, explanation if not reconciliation of the conflicting views concerning radiotherapy of breast cancer seems possible The cause of death from this disease is distant spread of metastases rather than local persistence except in very rare instances. Failure of treatment to effect cure must be due to distant spread of disease before during or after treatment When distant metastases become evident after treatment it is not possible to say at what time the spread actually occurred When distant metastases have occurred before the time of diagnosis and treatment all forms of treatment will be equally ineffective in producing cure. If this circumstance is the common cause of failure a similarity in survival rates and cure rates achieved by different treatment policies is to be expected

Surgery and radiotherapy singly or in combination are offered in the hope of improving the chance for cure or survival but they are local treatments capable only of local effects Comparison is possible only on a basis of effectiveness in eradicating or controlling disease in the area to which they are applied A useful basis for comparison would be 1) control of disease on chest wall and in axillary and supraclavicular regions, 2) mortality and morbidity 3) anatomical defect 4) functional impairment, 5) lymphedema, 6) radiation sickness and reaction To date information has not been analysed in this fashion

The Concept of Dose in Radiation

"The roentgen shall be the quantity of X or gamma radiation such that the associated corpuscular emission per 0 001293 gram of air produces, in air ions carrying 1 electrostatic unit of quantity of electricity of either sign (3) "

The roentgen is a physical unit for measuring the energy released through the interaction of radiation and matter It is emphasized that the roentgen is a physical unit. It is not a statement of dose that can be directly related to an effect upon living tissue An ionization chamber exposed to radiation may register a given number of roentgens a minute or a month Although the effect is the same upon the inert ionization chamber a given amount of radiation delivered to living cells in one minute will have a very different effect if delivered to the same tissue in a period of a month

Radiation administered may be recorded as air dose skin dose or tissue dose When an effect is desired at a given site, the dose at this site should be determined if dose and effect are to be predicted or related

Air dose is the intensity of irradiation recorded by an ionization chamber suspended in air at a fixed distance usually 50 cm from the target of an X ray tube The intensity of irradiation will diminish according to the inverse square law as the ionization chamber is moved further away from the target of the X ray tube It is therefore important that the point at which the measurement is made be clearly stated

Skin dose is known also as air dose plus backscatter This is determined by placing the ionization chamber either on skin or half imbedded in the surface of the unit density material at a fixed distance from the X ray target usually 50 cm Even though the

ionization chamber is maintained in exactly the same position with reference to the target of the X-ray tube, the addition of the patient or some comparable material back of the ionization chamber will increase the amount of radiation registered by the ionization chamber. When radiation strikes matter, a portion of the primary radiation is scattered and secondary radiation is produced. Some of this passes in a backward direction and therefore will increase the amount of radiation incident on the ionization chamber. This is known as backscatter. Backscatter is proportionate to the area of the field exposed to radiation. Thus, for the same dose in air, the dose in skin will be greater for a large field than for a small field.

Tissue dose, tumor dose, and depth dose are synonymous for dose measured at a point below the surface of the body. This is usually expressed in tables or charts as a percentage of either air dose or skin dose. Compared to either of these values, it will be diminished according to the inverse square law since it is farther away from the X-ray tube, and diminished also by absorption of radiation in the intervening tissue. It will be increased by scattered radiation from surrounding tissue on all sides of the point of measurement.

Air dose, skin dose or tissue dose are all statements of the amount of radiation at a point, whether this point be in air, on skin, or within the body. This, however, does not give complete information as to radiation throughout the tissue irradiated any more than a single light reading with a light meter would give all information about the lighting in a room. If, for any reason, there is considerable variation in the intensity of radiation throughout the irradiated area, it may be necessary to give the maximum and minimum dose. More complete information requires that a dose distribution diagram be prepared which is in essence comparable to a contour map from which the altitude at any point can be read.

When we prescribe a dose of radiation, we are relating amount of radiation in roentgens to a biologic effect that we wish to produce. In prescribing dose, therefore, these features must be borne in mind: 1) the amount of radiation should be determined at the site where a given effect is desired, 2) radiation is not uniform, and maximum and minimum dose should be given, 3) a statement of roentgens alone is not a statement of dose unless the time required for delivery is noted, 4) the tolerance of normal tissue diminishes as the area of skin exposed to radiation increases. These technical factors should be given as part of the prescription: the size and number of treated fields, the target skin distance and the quality of radiation. Quality of radiation may be adequately expressed as half value layer. Half value layer is the thickness of aluminum or copper which will diminish the intensity of the beam by 50 per cent. The same information is given by a statement of the kilovoltage and filter used.

Treatment Policy

A general appreciation of the problem of breast cancer has considerable influence on the treatment policy and the techniques for treatment by radiation. Because of the suspicion that the commonest cause of failure in the treatment of breast cancer is distant spread of disease before the time of diagnosis and treatment, radiotherapy is not undertaken with the sole purpose of improving cure rates. The eradication, control or prevention of recurrence of disease on the chest wall or in the immediate lymphatic drainage areas is of great importance to the patient whether or not distant metastases are present. This is the primary aim of treatment.

Breast cancer is, as a rule, moderately sensitive to radiation, yet, it is not suffi-

ciently sensitive that one could hope for a cancerocidal dose which will be well within the tolerance of normal tissue It is necessary to give the maximum dose which will be tolerated in the treatment areas It is essential to observe the tolerance of normal tissue because exceeding tolerance will not guarantee cure and may even jeopardize the chance for successful local control If failure most often results from distant spread of disease before treatment is instituted cures cannot be increased by higher doses of radiation administered locally Whether or not cure results, local control of disease is still important Whenever the probability of local persistence or recurrence after mastectomy is high radiotherapy may improve the chances of local control This is the basis for the following outline of policy

Operable Breast Cancer with No Evidence of Lymph Node Metastases on Pathologic Examination

Postoperative radiotherapy is not recommended When the disease is confined to the breast the chance for cure is high and the likelihood of recurrence on the chest wall and in the lymphatic drainage areas is low It is recognized that this will occur occasionally but it is not deemed justifiable to subject all such patients to postoperative radiotherapy when only a minority have possible benefit

Operable Breast Cancer with Metastases To Axillary Lymph Nodes Demonstrated by Pathologic Study

There are three policies that could be proposed in this circumstance

a No routine postoperative radiation treatment is withheld until such time as persistent or recurrent disease becomes evident This policy would spare some patients unnecessary radiation but for those patients who did develop recurrent disease failure to utilize a standard prophylactic measure might be considered neglectful

b Postoperative radiation might be offered to those patients who have extensive ' axillary lymph node involvement The extent of recognized axillary involvement depends upon painstaking dissection search for lymph nodes and study of serial sections In the face of such variables it would be difficult to apply this policy in a uniform fashion

c Postoperative radiotherapy is given to all patients with proven metastases in axillary lymph nodes. This is the recommended policy

Inoperable Breast Cancer

This category includes a) patients with extensive disease on the chest wall and in the axilla to an extent not within the criteria of operability (see Chapter XI) b) those with evident metastases to the supraclavicular or internal mammary region (5) c) patients with distant metastases at the time first seen d) patients with operable lesions but who by virtue of other disease or advanced age are ineligible for radical mastectomy e) those with operable disease who refuse operation

The first consideration in recommending treatment of patients in this group is the nature of presenting manifestations. In some patients the primary breast lesion may require treatment because of bulk or breakdown even though there are distant metastases. In other patients the primary lesion in breast may be relatively insignificant but distant metastases, whether in bone pleura or peritoneal cavity may be treated because of the patient s discomfort

If it is technically feasible and clinically advisable, simple mastectomy followed by radiotherapy is recommended for inoperable breast cancer even in the presence of limited

distant metastases By this means the patient is offered an excellent chance of control of the evident disease for the duration of life Radiotherapy may be carried out more thoroughly and with less discomfort to the patient following removal of the bulk of the disease

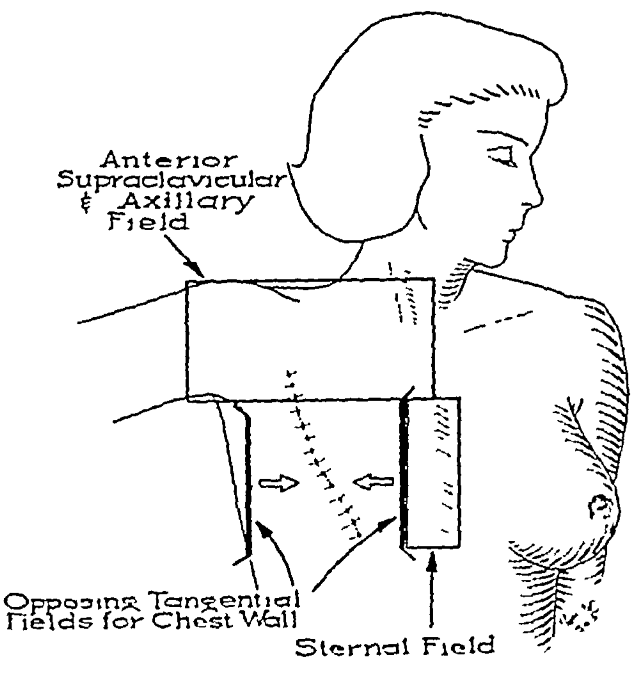
Treatment of the primary breast cancer by radiotherapy alone is recommended: a) when simple mastectomy is impractical for technical reasons, b) when the extent of distant metastases is such as to render the operation of simple mastectomy unjustifiable, c) when the patient refuses surgery of any kind

Sterilization is never advocated as a routine or prophylactic measure for a patient with breast cancer in the premenopausal period Sterilization by pelvic radiation is recommended routinely for patients in the premenopausal period who show evidence of distant metastases either at the time of diagnosis or who develop these at some time in the postoperative period

When pleural or peritoneal effusion occurs and tumor cells are identified in the effusion, the use of radioactive colloidal gold is indicated Disseminated disease involving skeleton, soft tissues, or both, is an indication for hormone therapy This is a systemic form of treatment that may particularly benefit the patient's sense of well being It may be combined with local radiotherapy to a presenting manifestation such as a painful bone lesion or a progressive metastasis involving soft tissue

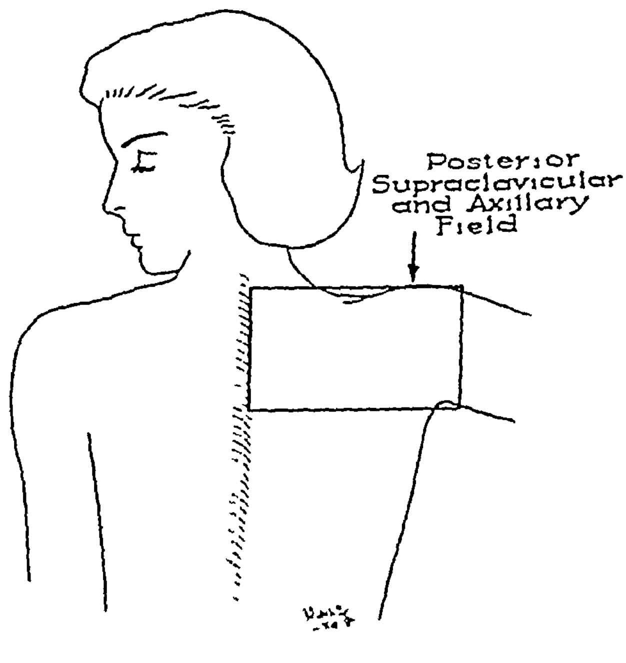
Treatment Techniques

An ideal technique for radiation for breast cancer would deliver a uniform dose throughout the cancer bearing area This would be simple to duplicate from day to day, and it would be applicable to all patients Treatment of the primary site and the adjacent



a

Fig. 125A Arrangement of treatment fields for chest wall, internal mammary region, and anterior aspect of supraclavicular and axillary regions



b

Fig 125B Posterior field for supraclavicular and axillary regions is directly opposed to the anterior field shown in Fig 125A

lymphatic drainage areas is sometimes attempted as a single unit From the grossly irregular contours involved it is evident that a simple arrangement of fields cannot give uniform radiation, and a complex plan will lead to a very difficult problem in determining dose The alternate approach is to divide the entire region to be treated into two or more separate but matching units This permits a more precise control of dose in any one unit but there is some hazard of excessive or inadequate dose along the matching margins Despite this hazard treatment of the area in several units has the advantage of simplicity for duplication from day to day and from one patient to another and permits flexibility for modification under different circumstances In so far as possible in the techniques described, the size and arrangement of treatment fields are constant and the time for the course of treatment is fixed The aim is to facilitate the development of skill in duplicating both the technical procedure and the biologic effect

The entire region is divided into three areas the chest wall, the supraclavicular and axillary regions treated as a single unit and the internal mammary region (figs 125 A and B 126 127 A, B, C D)

The chest wall is irradiated with opposing medial and lateral X ray beams which are therefore tangential to the chest wall Di

Fig 126 The fields shown in Fig 125A are outlined on a patient

distant metastases By this means the patient is offered an excellent chance of control of the evident disease for the duration of life Radiotherapy may be carried out more thoroughly and with less discomfort to the patient following removal of the bulk of the disease

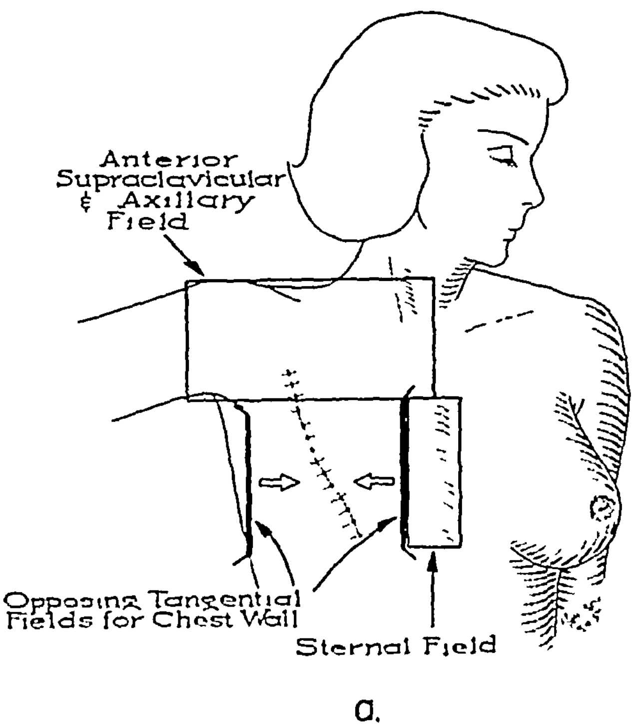
Treatment of the primary breast cancer by radiotherapy alone is recommended· a) when simple mastectomy is impractical for technical reasons, b) when the extent of distant metastases is such as to render the operation of simple mastectomy unjustifiable, c) when the patient refuses surgery of any kind

Sterilization is never advocated as a routine or prophylactic measure for a patient with breast cancer in the premenopausal period Sterilization by pelvic radiation is recommended routinely for patients in the premenopausal period who show evidence of distant metastases either at the time of diagnosis or who develop these at some time in the postoperative period.

When pleural or peritoneal effusion occurs and tumor cells are identified in the effusion the use of radioactive colloidal gold is indicated Disseminated disease involving skeleton, soft tissues, or both, is an indication for hormone therapy This is a systemic form of treatment that may particularly benefit the patient's sense of well being It may be combined with local radiotherapy to a presenting manifestation such as a painful bone lesion or a progressive metastasis involving soft tissue

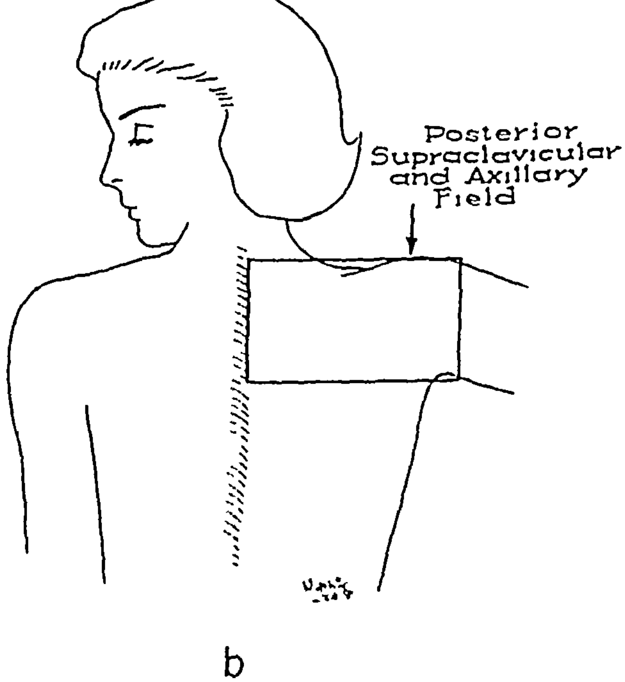
Treatment Techniques

An ideal technique for radiation for breast cancer would deliver a uniform dose throughout the cancer bearing area This would be simple to duplicate from day to day, and it would be applicable to all patients Treatment of the primary site and the adjacent



a.

Fig. 125A Arrangement of treatment fields for chest wall, internal mammary region, and anterior aspect of supraclavicular and axillary regions



b

Fig. 125B Posterior field for supraclavicular and axillary regions is directly opposed to the anterior field shown in Fig 125A

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The chest wall is irradiated with opposing medial and lateral X ray beams which are therefore tangential to the chest wall Di

Fig 126 The fields shown in Fig 125 A are outlined on a patient

FIG 127

A The patient is in position for treatment of the medial of the two opposing fields for the chest wall The beam is horizontal, and the patient is propped into the desired oblique position To treat the lateral chest wall field, the patient's position is not disturbed, but the table is simply turned through 180 degrees

B Bolus material is added A back plate is being used to aid in accurately directing the beam, and to retain the bolus material

C The patient is in the supine position for treatment of the anterior supraclavicular and axillary field For the posterior field (fig 125B) the patient lies in the prone position

D The supraclavicular fossa and axilla have been filled in with bolus material

rect fields to the chest wall are avoided in so far as possible By sparing the underlying lung and restricting the total volume of tissue irradiated, radiation pneumonitis is avoided When radiation is delivered through tangential fields to a curved or irregular surface, dose can be determined only by direct measurements in each individual case A uniform and predictable distribution of dose may be obtained by the use of bolus material Bolus material is any unit density substance such as whole rice or rice flour

enclosed in small cloth or plastic bags which are used to build the irregular part into a solid block for the uniform absorption and scatter of the radiation

The axilla and supraclavicular regions are radiated as a single unit through opposing anterior and posterior fields Again bolus material is packed in the supraclavicular region and in the axilla to build these irregular volumes up to a uniform block of unit density

The third zone is the region of the internal mammary lymph node chain This is irradiated through a single narrow field directed into the mediastinum (figs 125 A and B 126)

These three zones are matched with all possible care If the margins overlap there may be an area of over radiation or if the margins are not approximated a skip area may receive little or no radiation With slight modification a basic treatment plan built around these three units can be adapted for postoperative treatment following either radical mastectomy or simple mastectomy or for treatment of the intact breast

Treatment Factors

Kilovoltage

Conventional 'deep 'X ray therapy equipment is energized at 200–250 kilovolts This refers to electrical potential applied to the X ray tube from the transformer The greater the kilovoltage the greater is the average energy of the X rays produced and the shorter is the average wave length or in popular terms the harder or more penetrating are the X rays.

Filtration

A filter usually of copper 0 5 to 3 mm in thickness, is always added The softer" X rays of long wave length tend to be absorbed by the filter so that the transmitted X ray beam is more penetrating because its average wave length is shorter In the process of filtration the output in roentgens per minute is decreased and treatment time therefore will be prolonged A compromise must be reached between maximum filtration and economy of treatment time This will depend upon the adequacy of equipment and the judgment of the therapist

Half value layer (HVL)

This is an expression which denotes the quality of hardness of the X ray beam It is expressed in mm of copper (or other substance) which is necessary to diminish the intensity of an X ray beam by one half The greater the penetration of an X ray beam or the shorter the average wave length the greater the thickness of copper required to diminish the intensity to one half The quality of an X ray beam is due to the kilovoltage and the filtration but it can be expressed adequately and succinctly in terms of its HVL alone

Treatment distance

This is also called target skin distance (TSD) It must be recorded because the intensity of the X ray beam diminishes with increasing distance according to the inverse square law A treatment distance of 50 cm is most commonly used Tumor dose would be increased by using a greater TSD but this would also diminish intensity and increase treatment time

Elapsed time

This is the total time in days or weeks inclusive of the first and last treatments As a factor in prescription it implies that if treatment is not interrupted a predicted radiation reaction will result In the following treatment techniques a constant elapsed time of three weeks has been adopted With

FIG 128A

FIG 128B

FIGS 128A and B Large fungating carcinoma of the right breast considered "categorically inoperable" Patient treated by radiotherapy alone with excellent palliative result Two years after the onset of treatment patient remains comfortable and without evidence of distant metastases

distant and undiscovered metastases in inoperable breast cancer, it would not seem reasonable to offer treatment to the supraclavicular region and to the internal mammary region if there is no demonstrable or symptomatic disease in these regions Commonly, there will be a bulky mass occupying the breast or axilla, possibly with breakdown or ulceration, or with lymphatic obstruction involving the arm The intention here will be to diminish the bulk of the lesion, to produce healing of an ulcerated or bleeding lesion or to relieve lymphatic obstruction If there is an ulcerated or bleeding lesion of the breast with only minimal axillary and supraclavicular lymphadenopathy, treatment may be "
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less and a lower dose in roentgens may be delivered to the tumor The second consideration is that for inoperable disease particularly if there is any evidence of distant metastases, the severity of the local reaction should be proportionate to the total benefit for the patient. A reaction that would increase the patient s discomfort much beyond that of the disease itself would not be justifiable For both these reasons although a maximum dose of 3 500r and a minimum dose of 3 000r in three weeks may be appropriate and safe this dose might be diminished by ten or 20 per cent for bulky lesions, or for individuals with relatively advanced disease

Supervoltage Radiation

The term supervoltage refers to X rays generated at one million volts or more or to the gamma radiation of the recently developed cobalt-60 units As facilities for this type of radiation become available possibilities for its use in the treatment of breast cancer should be defined Views currently held vary from new hope for cure to rejection because no increase in cures is likely The governing factors have already been outlined in this chapter The chance for cure lies in the nature and extent of the disease rather than in the modality for treatment The limitations of supervoltage radiation are those common to all types of radiation it is a local form of treatment which is clinically useful to produce a local effect if there is an advantageous relation between normal tissue tolerance and tumor radiosensitivity

The advantages of supervoltage radiation are these

1 Skin tolerance is no longer a limiting factor in achieving a desired tumor dose Maximum ionization is reached several millimeters deep to the surface Therefore the dose on skin necessary to achieve a given tumor dose is less than with conventional 250 Kv X rays, and skin reactions are mild With two million volt X rays (HVL 6 mm lead) a minimal erythema is produced in a five cm circular field by 2 000r in a single dose

2 Because of greater penetration and lesser skin reaction, deeply located tumors can be treated with smaller and fewer fields Therefore treatment plans are simple and treatment time can be diminished For instance postoperative radiation for breast cancer can be given with only three fields two opposing fields on the chest wall having a separation up to 24 cm., and a single anterior supraclavicular and axillary field

3 For a given tumor dose less energy is absorbed by all the tissues in the radiation beam and treatment is tolerated better by the patient

4 Radiation of this energy tends to be absorbed equally in tissues of different densities, whereas 250 Kv X rays are absorbed to a much greater degree in bone Because of this selective absorption of conventional 250 Kv X rays dose in bone may be 200 per cent greater than in the adjacent soft tissues This factor is responsible for the hazard of bone necrosis which is greatly lessened with high energy radiation

The ease with which a desired dose may be delivered with minimal discomfort means that treatment may safely be offered to more patients In particular, it means that an effective dose of radiation may be given to lesions of inoperable cancer with minimal risk of complications Effective treatment may be extended to widespread disease on the chest wall to deeply located metastases in bone and even to pulmonary and liver metastases.

These advantages do not promise more cures but they are an essential part of complete facilities for the management of cancer The supervoltage unit is to radiotherapy

what the blood bank is to surgery Transfusions cure no cancer but they make treatment possible by reducing the risk involved, thereby contributing to the management of the patient and influencing the possibility of cure or increased survival

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CHAPTER XVI

Hormonal Alterations in the Palliative Treatment of Advanced Breast Cancer

ROBERT A HUSEBY, M.D, PH.D

Although it has been almost 60 years since it was first demonstrated that alterations in the endocrine system of patients suffering from breast cancer could result in regressive changes in this type of malignant neoplasm, it has only been during the last decade or so since potent hormone preparations have become generally available, that appreciable progress has been made in the exploration of the usefulness of endocrine alterations in the treatment of this serious disease It is, therefore not surprising that at the present time although a considerable body of information is available attesting to the general phenomenon of breast cancer regression following a variety of endocrinological alterations, many of the most pertinent questions regarding these modalities of therapy remain unanswered In spite of this serious deficiency in fundamental information hormone therapy has become a useful addition to our therapeutic armamentarium in the palliative treatment of those unfortunate persons suffering from advanced and incurable breast cancer When properly employed hormone therapy can add considerably to their relative well being and probably also to their period of survival

The experience of the past years has definitely proven that the progressive growth of breast cancer frequently can be altered or reversed by appropriate alterations in the hormonal environment in which the cancer finds itself In spite of many instances of most dramatic disappearance of the clinical manifestations of breast cancer following endocrinological alterations the disease usually succeeds in adapting itself to its new environment and eventually causes the death of the patient unless some fatal intercurrent disease or accident intervenes It is, therefore well established that all types of hormone therapy for this disease are time limited in their effectiveness and should be employed only after curative measures have failed or are no longer applicable to the particular clinical situation confronting the patient and the physician Furthermore each type of effective hormone alteration is associated with certain unpleasant and even dangerous general effects to the patient so that these modalities of therapy must be used wisely and with considerable knowledge if they are to result in effective palliative treatment In the following pages an attempt will be made to place our present day knowledge of hormone therapy in a proper

prospective so that the best use can be made of these methods of treatment.

Interruption of Gonadal Function

Following the report by Beatson in 1896 of the beneficial effects of oöphorectomy in patients with far advanced breast cancer, the usefulness of this procedure in the palliative treatment of this form of cancer was extensively disputed and rather generally discredited This is not surprising when one recalls that this initial pioneer publication antedated the ellucidation of the very concept of hormones by some six years and that good roentgenological methods for following the course of metastatic deposits in the bony skeleton and within the thoracic cage did not become generally available until about 20 years later In reality it has been only since the rather recent increase of interest in the relationship of hormones to established breast cancer that the usefulness of interrupting ovarian function as a means of treatment of advanced breast cancer has received wide acceptance, and even today there remains some discussion as to when, and under what circumstances, this procedure affords the greatest benefit to the patient.

It is now clearly established, however, that in women who are experiencing regularly recurring menses varying degrees of improvement will follow the interruption of normal ovarian function in a significant proportion of the cases In approximately one third of the pa[illegible] is where the bony

Strange as it may seem, subjective improvement, usually rather transient may also occur in patients in whom no radiographic evidence of improvement occurs and even in some instances where progression of the disease continues unabated Significant regressions of the primary tumor, if present, and of metastatic deposits involving the soft tissues of the body also occur following this type of endocrine alteration Primary tumor masses may decrease measurably in size and at times become no longer demonstrable clinically as may also metastatic deposits in lymph nodes, subcutaneous tissues, lungs and pleura Unfortunately, the duration of the remission effected by this method of therapy is usually measured in terms of months and the number of patients who remain in remission significantly over a year are in the minority

As patients approach and enter the climacteric, the frequency with which ablation of ovarian function results in a significant and measurable regression of tumor deposits decreases significantly Precise information as to the overall usefulness of such procedures in the treatment of the recently "post-menopausal" woman is at pres[illegible] ailable, but th[illegible] gs of Sc[illegible] eloh that a l[illegible] tage of [illegible] of breast [illegible] an abn[illegible] 'asia of the [illegible] oma, wh[illegible] 'y functi[illegible] ure, req[illegible] inve[illegible] the pos[illegible] of c[illegible] etasta[illegible] in eff[illegible] or

ble This latter factor is frequently of considerable importance particularly in cases suffering from widespread, debilitating and very painful disease It is not uncommon for a patient to experience significant and even remarkable relief of pain within a few days or a week or so following oöphorectomy Such experiences amply justify the transient morbidity associated with this relatively minor surgical procedure One tends also, to favor this method of treatment in patients who are under 40 years of age where larger doses of irradiation are required to effect adequate ovarian suppression In patients beyond this age particularly those who present a less acute situation, adequate pelvic irradiation appears to be a suitable therapeutic procedure. It should be stressed however that relatively low doses of irradiation may lead to amenorrhea and yet be inadequate to produce sufficient suppression of ovarian function to effect tumor regression It is generally recommended that 600 to 1,200r be delivered to the mid pelvis in a period of ten days or less in order to accomplish sufficient ovarian suppression for this purpose, and if pelvic irradiation is to be employed in younger women, somewhat higher doses should be administered. As far as one can tell from a review of the literature, tumor regression following adequate ovarian irradiation occurs as frequently as following surgical extirpation of the ovaries. There is as yet no comparative data as to the relative longevity of the favorable responses obtained by these two modalities, but it is fairly definitely established that between one and two months must elapse following ovarian irradiation before the level of urinary estrogen falls to post-castration values and in certain patients considerable fluctuation in the excretion of estrogens may occur for many months following ovarian irradiation

In anticipation of the consideration of other types of hormone therapy which is to follow it should be pointed out that the general sequelae of "castration" are relatively few To effect this type of therapy the patient is not required to visit the office of her physician frequently She will generally experience symptoms characteristic of the climacteric to a greater or lesser degree depending somewhat upon her age, but we have been impressed by how well this group of patients adjusts to these minor unpleasantnesses when the situation is fully explained to them In our experience mild sedation is required only relatively infrequently for the control of nervousness, and the resultant vasomotor phenomena are generally viewed rather philosophically by those patients who obtain a good therapeutic response as far as their tumor is concerned It is obvious that estrogenic hormones must not be employed to control the resultant subjective symptomatology, and only in the very extreme cases should small doses of androgenic hormones be employed for symptomatic relief Full therapeutic doses of these compounds may be required at a later date in an attempt to control the neoplastic process.

A subject of some disagreement concerns the usefulness and advisability of *prophylactic* castration Whether or not performing an oöphorectomy at the time of the primary curative surgery results in an increase in the number of patients remaining free of recurrent or metastatic disease five and more years after therapy has not yet been completely established Advocates of this procedure have published results obtained in several relatively small series of cases, each suggesting an improvement in the over-all survival in younger women who were menstruating regularly at the time they developed their primary breast tumor On the other hand oncologists in most of

the larger centers in this country feel that this procedure results in no improvement in the five year "cure" rate and prefer to reserve it until evidence of recurrent and/or metastatic disease appears At this time it may be required as an important therapeutic adjunct To date no one has published a carefully controlled series of cases to prove or disprove these divergent viewpoints It is, however, generally believed that women who have had a cancer of the breast should not, subsequent to their primary therapy, become pregnant (Chapter XVII). This is particularly so in those patients who had lymph node involvement at the time of radical mastectomy since about 70 per cent of such patients may have foci of tumor beyond the area excised, and the hormonal alterations incident to pregnancy have been noted frequently to stimulate such quiescent tumor deposits into active growth

Although cancer of the male breast is not frequent in its occurrence, the results of surgical therapy in most clinics are somewhat poorer than those obtained in cancer of the female breast (Chapter XX) This results, in all probability, from a greater tendency for men with this disease to delay seeking medical advice It is, therefore, fortunate that castration of the male patient results in very effective palliation with considerable regularity Although there are no large series of cases published, it would appear that, in up to two thirds of male patients so treated, significant tumor regression and palliation is obtained As in the case of cancer of the prostate, the age of the patient does not seem to influence the excellence of the response obtained Tumor deposits in all tissues of the body seem to respond with about equal frequency, and the length of the resulting remission is, in general, considerably longer than in the case of ovarian ablation in females In fact, periods of remission ranging from two to five years are not particularly uncommon. In spite of the generally favorable results obtained with this type of therapy, it is obvious that the primary attack upon this disease should still be radical surgical extirpation where feasible, and orchiectomy should be postponed until evidence of recurrent or metastatic disease appears Furthermore, testicular irradiation is not a desirable method of therapy since the testicular interstitial cells appear to be relatively radio-resistant, and the moist skin of the scrotum tolerates irradiation poorly

Administration of Androgenic Hormones

The administration of androgenically active steroids to women with advanced breast cancer is perhaps the most widely used of the endocrinologic procedures designed to control the growth of this disease The extensive use of this class of hormones has resulted from the prevalent concept that if estrogenic hormones are in some measure causal in the development of breast cancer, then the use of large doses of androgenic hormones might be expected to reverse the process or at least to slow its rate of growth However, the fact remains that, although the administration of androgenic hormones has been found to be useful in the palliative treatment of advanced breast cancer, the percentage of patients who show objective improvement as a result of therapy is smaller than is the case with the interruption of ovarian function in pre-menopausal women or with the administration of estrogenic hormones to older post-menopausal women Striking subjective improvement in the absence of objective evidence of tumor regression is, however, a definite asset in the treatment of patients with androgens

The most striking results following the administration of androgens tend to occur in women who have metastatic involvement of the bony skeleton Relief of bone pain frequently occurs within one to two weeks after therapy has been instituted and is usually associated with an increased sense of well being and an improvement in the patient's general physical status Such symptomatic improvement resulting in varying degrees of rehabilitation, is generally reported to occur in about two thirds of the patients treated However, it is frequently to be seen in patients whose metastatic disease progresses unabated despite treatment so that roentgenographic evidence of actual healing of the areas of metastatic involvement is to be observed in only about one-fifth of the cases In this latter group, extensive lytic lesions decrease measurably in size and even may heal completely, most often leaving an area of bone sclerosis to mark the previous area of osteolysis. Although roentgenographic evidence of bone repair usually requires from two to three months to become evident chemical evidence of such repair is almost always manifested earlier than this and consists of a decrease in the urinary excretion of calcium and phosphorus and a tendency for the serum alkaline phosphatase to rise if it was not already considerably elevated prior to the beginning of therapy Uncommonly in certain patients regression of some skeletal lesions may occur at the same time that other skeletal lesions may be progressing or even as new bone lesions are appearing.

Improvement in metastatic deposits involving the soft tissues of the body tend to occur somewhat less dramatically than is the case with skeletal lesions Again about one-fifth of women with metastatic and/or recurrent involvement of the superficial soft tissues of the body show measurable improvement, but such improvement tends to occur rather slowly over a period of several months. Regression of recurrent and/or metastatic disease involving the skin subcutaneous connective tissues and lymph nodes seems to occur with a slightly greater frequency than does the regression of large locally inoperable primary tumors Unfortunately, metastatic disease involving the lungs and pleura seems to respond poorly to androgenic therapy, for usually only five to ten per cent of patients with such pulmonary lesions will show definite evidence of regression Metastatic disease involving the abdominal viscera has also been known to respond favorably to this type of treatment, but any statement as to the exact percentage of patients so responding is impossible because of the difficulty in diagnosing and following the response of such lesions. Few favorable responses in patients with intracranial lesions have been recorded

Unlike disruption of ovarian function and the administration of estrogenic hormones, the age of the patient does not seem to be a very important factor in the response obtained with the administration of androgens Regression of disease occurs in a significant proportion of patients in any age group although the number of patients responding favorably may be very slightly higher in women over 60 years As with all other forms of hormone therapy for this disease the remissions induced are time limited In almost 60 per cent of those showing an initial regression the tumor deposits will have again begun to progress by the sixth month after initiation of therapy and in spite of continued therapy, this rate of reactivation rises to between 85 and 95 per cent by the end of one year When the disease has reactivated in the face of continued therapy withdrawal of the androgen sometimes results in a second

regression of the tumor deposits Unfortunately, the regressions seen following withdrawal of the hormone are usually lesser in degree and shorter in duration than was the case with the primary regression

Effects of androgen administration other than the sought-for suppression of tumor growth invariably manifest themselves in patients being treated with the relatively large doses of hormone required Annoying to the patient is the development of various symptoms of masculinization which tend to increase in their severity as therapy is continued Although many patients do not show all of the following signs of masculinization, most patients treated for three months or more will exhibit some of them The texture of the patient's skin tends to become coarse, and her complexion may become distinctly ruddy with a rather typical acne frequently developing on the face and upper trunk Hirsutism of varying degrees, depending somewhat upon the patient's racial background and coloring, frequently occurs also and may be accompanied by the development of temporal alopecia A deepening and coarsening of the voice occurs in a large percentage of women treated, and when therapy is continued for many months, visible changes in the vocal chords and larynx may occur leading to voice changes similar to those seen in boys during puberty In general, all of these manifestations will regress slowly after therapy has been discontinued A side effect of androgen administration, which occurs with considerable frequency and which can become very unpleasant particularly to unmarried and widowed women, is an increase in libido This is always of the female type, and possibly results from an enlargement of the clitoris and an increased sensitivity of the external genitalia secondary to vascular changes This symptom, at times, becomes sufficiently unpleasant that the patient may request that therapy be discontinued Fortunately, the process generally regresses after treatment is stopped

In addition to the above mentioned undesirable side effects, two effects of therapy which may endanger the patient's life occur fortunately with considerably less frequency In approximately ten per cent of the individuals in which the metastatic process involves the skeleton, but almost never in patients whose disease is confined to the soft tissues of the body, a significant and dangerous elevation of serum calcium is observed When this complication is the result of therapy, it usually appears after several weeks or even after two to three months of treatment and manifests itself clinically by the onset of nausea, vomiting, anorexia, apathy, weakness and drowsiness which in severe cases can proceed to mental disorientation, stupor, coma, vascular collapse, renal failure and death It is, therefore, most desirable to determine the serum calcium level in all patients with bony metastases prior to the institution of androgen therapy, and to repeat this determination should any of the above mentioned symptoms arise during the course of treatment In the event that hypercalcemia develops, the hormone must be stopped immediately and proper methods of supportive therapy instituted, these consist primarily of adequate hydration and electrolyte replacement where vomiting has been excessive If the patient is stuporous, 2 5 per cent sodium citrate may be administered intravenously in an attempt to bind the excess of free calcium, although care must be taken in such therapy not to induce alkalosis since varying degrees of renal insufficiency frequently are associated with the development of hypercalcemia After the serum calcium levels have returned to a normal range, hormone therapy with the

same or with another hormone may be cautiously restarted if it has been demonstrated that the patient's kidney function is essentially normal Hypercalcemia occurs more often in patients whose skeletal disease is progressing rapidly either because of or in spite of hormone therapy and is frequently associated with a certain degree of renal dysfunction which is rapidly made worse as the result of calcification of the renal tubules Hypercalcemia also occurs spontaneously in cases of untreated breast cancer where the skeleton is extensively involved with a lytic process and this in itself does not contraindicate the use of hormones in the attempt to control the metastatic process. In cases of spontaneous hypercalcemia, considerable care must be exercised in starting hormone therapy, but when tumor regression results from treatment, the hypercalcemia generally abates Unfortunately, there are no reliable chemical tests which will forewarn the physician of the development of hypercalcemia during the course of treatment with hormones

The administration of androgenic hormones regularly leads to a retention of body fluids. When younger women are being treated a weight gain usually of from five to ten pounds frequently occurs during the first month or so of therapy The development of dependent edema does not occur frequently in women 50 years of age or under and when therapy is discontinued a diuresis with a concomitant loss of weight usually occurs within two weeks When older women with less cardiovascular reserve are being treated edema develops considerably more frequently In such instances appropriate steps must be taken to control the retention of fluid in order to avoid precipitating cardiac decompensation This problem will be discussed more completely in the section dealing with estrogen therapy

Considerable investigation has been carried out in an effort to determine which androgenic compounds have the greatest effect on tumor suppression and in what dosage schedules It would be most desirable quite obviously, if a compound or a dosage schedule could be found that was effective in suppressing tumor growth and yet have little or no masculinizing side effect. ' As yet no such compound or dosage schedule has been discovered Testosterone propionate in oil injected intramuscularly in the amount of 50 mg three times weekly has been found to be an effective tumor suppressing agent and equal to any preparation so far tested Although larger doses than this had previously been considered as being optimal present evidence would indicate that neither smaller nor larger amounts of this particular preparation are any more if indeed as, effective as this now standard dosage. Stanolone injected intramuscularly three times weekly in the dose of 100 mg per injection appears to be equally effective as a tumor suppressing agent but, contrary to original hopes it also appears to be essentially as masculinizing as 50 mg of testosterone propionate three times weekly with the possible exception that somewhat fewer women experience a severe increase in libido Whether or not smaller doses of stanolone will give as good therapeutic results with lesser degrees of masculinization has not yet been determined Orally administered methyl testosterone in the dose of 100 mg daily also yields good therapeutic results and does emancipate the patient to some degree from frequent visits to the doctor's office However this preparation is still rather expensive and occasionally results in the development of jaundice which usually clears promptly upon stopping the drug Longer acting androgen preparations appear to be effective therapeutic agents but carry the inherent danger that their

action cannot be readily interrupted should untoward side effects such as hypercalcemia develop Therefore, considerable care must be exercised in their use, and, in general, it seems unwise to employ them until the patient has had an adequate period of therapy with a short acting drug in order to determine that she is responding favorably to treatment To date, all preparations possessing low degrees of androgenicity also have shown reduced tumor retarding effects

Administration of Estrogenic Compounds

The regressive changes frequently seen in advanced breast cancer in elderly women following the administration of relatively large doses of estrogenically active compounds still remains one of the most enigmatic phenomena associated with this type of cancer which is notable for its bizarre behavior patterns Although it has been more than ten years since this seemingly paradoxical therapeutic regimen was first demonstrated to be effective, no experimental or clinical data have been presented to explain the mechanism by which these compounds exert their tumor suppressing action To date, the only rationale for their use lies in the clinical demonstration of their effectiveness In spite of this, the observations of the past years have afforded us abundant sound data to guide us in the empirical administration of these compounds, and at present their use constitutes one of the most effective means at our disposal for the palliative treatment of breast cancer under certain specific clinical conditions

The physiologic age of the patient with regard to the menopause, either naturally occurring or artificially induced, is of primary importance when considering the use of these compounds With few exceptions it has been amply demonstrated that their use must be restricted to women whose last menstrual flow occurred five or more years prior to the time that estrogen therapy is contemplated The chronological age of the patient does not appear to be very significant, for excellent regression of primary tumor or metastases occurs in relatively young women whose ovarian function was artificially interrupted five years or more prior to the institution of estrogen therapy It has also been observed with considerable frequency that the administration of these hormones to premenopausal or to recently post-menopausal women results in an acceleration in the rate of tumor growth more frequently than it does in a regression of tumor deposits. This is in sharp contradistinction to the situation in women five or more years past the menopause where acceleration of tumor growth occurs but infrequently (in only about one per cent of cases) Whether or not this arbitrarily arrived at five year period may be shortened in those women who have been surgically castrated has not yet been completely established, and a very cautious trial of estrogen treatment may be indicated in certain situations in such women where other forms of palliative therapy have failed

Almost equally as striking, and at the present time completely unexplained, is the difference in responsiveness to this type of therapy depending upon the location of the recurrent or metastatic disease Between 40 and 50 per cent of women of an appropriate physiologic age who have recurrent and/or metastatic disease involving the superficial soft tissues of the body will show a measurable decrease in the size of these lesions following the institution of estrogen therapy. These favorable responses range in degree from a definite diminution in size of the superficial tumor masses (with epithelialization of ulcerating lesions) to a complete clinical, but usually not microscopic, disap-

pearance of many or all of the superficial tumor masses Significant regression of large locally inoperable primary tumor masses occurs somewhat less frequently, usually in about 35 per cent of treated cases, and complete clinical disappearance of these large areas of primary disease is seen rather infrequently Similarly improvement in metastatic lesions involving the lungs and pleura occurs in approximately one third of the cases. However the regressions may be clinically complete and may be associated with a remarkable relief of respiratory symptoms when they are due to the pulmonary metastases In general however all tumor masses involving the soft tissues of the body regardless of their location will be observed to regress in those patients showing a favorable response to therapy This fact might suggest that the somewhat lower response rate noted in patients with inoperable primary disease and with involvement of the lung and pleura may be due to the somewhat greater frequency with which such patients first present themselves for treatment at a time when their general state of health is rather poor

In contrast to this relatively high rate of favorable response in patients with soft tissue neoplastic disease healing of metastatic lesions in the bony skeleton occurs in only 10 to 20 per cent of the patients treated In general evidence of bone repair occurs considerably more slowly than is the case with lesions involving the soft tissues of the body but this may be in part, a reflection of the fact that not only must the tumor mass decrease in size but the bony supporting tissue must begin to regenerate before roentgenographic evidence of improvement becomes manifest The relatively unfavorable response of skeletal metastases to estrogen therapy is frequently emphasized in patients who have involvement of both the soft tissues and the bony tissues of the body In such patients it is common to see the soft tissue disease regress dramatically while the areas of bony involvement progress apparently unaffected by the treatment Furthermore, it is not uncommon to see patients with no demonstrable bone disease develop such lesions which then progress even while their soft tissue disease remains in good control as the result of estrogen treatment Rather unlike the use of androgenic hormones in the treatment of skeletal metastases, with estrogen therapy the subjective response of the patient more closely parallels objective evidence of improvement and instances of marked pain relief in patients in whom the bone involvement progresses are less frequently seen

Although several striking examples of improvement of metastases involving the abdominal viscera have been recorded, the frequency with which such improvement occurs is impossible to estimate because of the difficulty in diagnosing small lesions in this area and of following their response after therapy has been instituted Improvement of metastases involving the brain also seems to occur very infrequently

It would appear that the remissions induced by estrogenic therapy tend to be somewhat more prolonged than those following the administration of the androgens. In general, the disease has begun to regrow in about 65 to 70 per cent of the cases that showed an initial regression by the end of the first year This rate of reactivation rises to about 80 to 85 per cent at the end of 18 months Although the disease apparently always eventually adapts itself to its new environment the average duration of response has been reported to be about 15 months. In a small number of cases the disease remains under control for from two to five years or longer As far as our own experience is concerned we have been able to see no correlation between the

degree of the initial regression and the period of time that it will be maintained. In some cases where a complete clinical regression has occurred, reactivation has become apparent within six months while in other cases of incomplete regression the induced remission has lasted for from one to four years. Even after regrowth of the tumor becomes evident in the face of continuing treatment, the average life of our patients has been about 14 months. Several factors referable to estrogen therapy may contribute to this somewhat surprisingly long duration of life following reactivation. All the lesions that were initially present may not reactivate at the same time and those that do regrow seem at times to progress at a relatively slower rate than was apparent prior to the institution of treatment. Furthermore, once reactivation has occurred, significant second regressions are seen in almost two thirds of the patients when the medication is discontinued. These second regressions are usually not as complete and are not maintained for as long a period of time as was the case in the primary response to treatment, but in a few cases where they have been maintained for several months a third period of regression has followed restarting of the hormone therapy.

Since many tissues of the body normally are influenced by estrogenic hormones, it is not surprising that numerous alterations other than changes in tumor growth manifest themselves during the course of estrogen administration. Almost immediately upon instituting therapy, slightly over half of the patients will experience varying degrees of nausea which may be severe enough to cause vomiting in about one fourth of the patients treated. Many patients will also complain of muscular aching and general malaise, but in most instances these annoying initial side effects are minimal and will subside and disappear within one to two weeks if the medication is continued. In those cases in which these initial side effects are particularly severe, they may be lessened by reducing the dose of the hormone and administering it just prior to the patient's retiring or by changing to an injectable preparation for the first two or three weeks of treatment. In a relatively small percentage of cases, however, these early symptoms will be sufficiently severe and protracted to necessitate abandonment of therapy.

As therapy is continued, other side effects are frequently noted. The areolae usually become reddened and tender; this redness gradually gives way to a brownish pigmentation and the areolar tenderness usually subsides after a month or so of treatment although the breast itself may become enlarged and distinctly more firm in texture. A brownish pigmentation may also appear in the axillary folds, along the linea alba and over the perineum, and pre-existing nevae may become more prominent and more deeply pigmented. Skin turgor generally improves, but occasionally patients will complain of a dryness and an itching of the skin or an increased brittleness of the finger nails and hair. With continuing estrogen therapy patients may also develop a mild or even a moderately severe degree of urinary incontinence which is usually experienced only in situations of physical stress, but which may be sufficiently severe to be extremely embarrassing to the patient. Uterine bleeding has not been a serious problem in our experience. As therapy continues, a significant number of patients will experience short periods of minor degrees of "spotting," but in only a relatively small per cent has this "break through" uterine bleeding become sufficient in amount to warrant the discontinuance of the medication for a two to three week period in order to allow a complete shedding of the endo-

metrium so that the hormone could then be restarted. Of those patients who have not had significant "break through" uterine bleeding about 50 per cent will experience withdrawal bleeding when the medication is discontinued. Such withdrawal bleeding usually has its onset from three to five days after cessation of treatment and although it may be relatively copious in amount and may last from between one to two weeks, seldom requires surgical intervention.

The most serious general consequence of the administration of estrogenic hormones in these relatively large doses is the retention of body fluids. Since one is employing this therapeutic regimen primarily in elderly women many of whom have a considerably reduced cardiovascular reserve, the retention of fluid secondary to hormone administration becomes a major problem for it may precipitate an episode of cardiac decompensation which, if not recognized early, may cause the patient's death. In approximately 40 per cent of the women treated demonstrable dependent edema will develop. In those instances in which the patient has no significant cardiac disease demonstrable minor degrees of edema are usually tolerated without deleterious effects. However when significant amounts of edema fluid accumulate or when even minimal edema is seen in patients who have significant cardiac disease immediate steps should be taken to combat it. The most effective method is that of sodium restriction and every attempt should be made to lower the daily ingestion of sodium to the 300 mg level. The use of ion exchange resins may be helpful in this attempt but when used over a several month period steps should be taken to augment the patient's potassium ingestion in order to avoid the development of hypopotassemia. Ammonium chloride administration and the use of mercurial or other diuretics may be of assistance in the control of this edema but are in themselves usually not sufficient to combat the fluid retaining effects of the hormones so that sodium restriction seems to be the first logical step toward improving the situation. Because of this real danger, it is obvious that patients who have had previous episodes of cardiac decompensation must be given these large doses of hormones only with the greatest care. It is also obvious that hormone therapy should not be resorted to in those cases with primary operable disease whose cardiovascular status precludes surgical intervention since the risk associated with hormone therapy in such patients probably is as great as that associated with surgery.

As in therapy with the androgenic hormones, hypercalcemia is occasionally encountered with the use of estrogens in those patients who have osteolytic lesions of the skeleton and the same steps should be followed in combating this complication as were outlined in the discussion of androgen therapy.

The effectiveness of several different estrogenic compounds has been investigated and the following preparations seem to possess essentially equal tumor suppressing effects.

Oral preparations	
Diethylstilbestrol	15 mg daily
Ethinyl estradiol	3 mg daily
Conjugated equine estrogens	30 mg daily
Dienestrol	15 mg daily
Dimethyl ether of diethyl stilbestrol	30 mg daily
Injectable preparations	
Estradiol benzoate	5 mg three times per week
Estradiol dipropionate	5 mg two times per week

Of the oral preparations there is little to recommend one over another except as regards their cost since at these dose levels all produce the initial uncomfortable side

effects listed above with about the same regularity Although initial nausea can be reduced by using the injectable preparations, when continued therapy is desired, they impose upon the patient the necessity of very frequent visits to the physician It has not yet been established whether continuous or discontinuous estrogen therapy gives the better results, however it has seemed to us best to continue therapy at the above outlined dosages as long as the patient's tumor remains controlled unless, of course, the development of significant side effects forces discontinuance of the medication It should be pointed out, however, that although the tumor occasionally resumes growth within a few weeks after discontinuing treatment, this is not invariably the case, and in many instances the induced remission will continue for several months after the hormone has been stopped It is also true that the reactivations of the disease that occur after stopping therapy frequently will again respond favorably to the resumption of therapy with exactly the same drug Since, however, we have seen few additional undesirable side effects develop with prolonged continuous therapy, in some cases for as long as 3 5 years, and secondary regressions occur frequently upon discontinuance of therapy when reactivation has occurred in the face of continued treatment, we tend to continue therapy wherever possible as long as the patient's disease remains controlled

Newer Endocrinological Procedures

Due both to the relatively recent increase in interest in the relationship of the growth of breast cancer to alterations in the "endocrine environment" and to the increasing availability of hormone preparations suitable for substitution and large dose therapy, inquiry into the effects of adrenalectomy, hypophysectomy and large dosage therapy with cortical steroids is actively being pursued throughout the world at the present time Although it is as yet too early to give any complete evaluation of these procedures in the management of advanced breast cancer, certain facts have already become evident

ADRENALECTOMY

It seems fairly well established that during the months following ablation of ovarian function some extragonadal tissue may, in certain women, begin to excrete significant amounts of estrogenically active compounds The adrenal cortex is generally believed to be one, if not the only, major source of such hormones, and on this premise bilateral adrenalectomy has been carried out Similar experimental procedures include adrenal shunt operations Control of surgically induced hypoadrenalcorticism has, with experience, been fairly well standardized, and the postoperative mortality rate from electrolyte imbalance has been reduced to a relatively low figure Although the number of cases so treated is not large, the data indicate that definite objectively demonstrable regressions of tumor deposits do occur and subjective improvement may occur in the absence of objective signs of tumor regression Insufficient time has elapsed since the introduction of adrenalectomy for the control of advanced breast cancer to give us much of an idea of the period of control to be expected, but because of the magnitude of the problems encountered in the postoperative management of such patients, the use of the procedure would seem best to be restricted at the moment to those situations in which the patient can be carefully followed by a physician who has had considerable experience in the care of the completely adrenal insufficient patient Because of this, and because the "Addison" patient becomes so completely dependent upon close medical supervision, it would be of great importance to be able to predict which patients would have a reasonable

chance of receiving benefit from this procedure With this view in mind one group of investigators has attempted to correlate the histological configuration of the tumor with the response obtained following adrenalectomy and believe that regression occurs almost exclusively in those instances in which the tumor has a definite glandular pattern Unfortunately other investigators have not been able to observe such a correlation More recently it has been suggested that a favorable response to adrenalectomy occurs exclusively in those patients who originally experienced significant regression following oöphorectomy To date, too few cases have been analyzed from this standpoint to know the value of this correlation but it seems obvious that such a correlation will be of little help in deciding which women should be considered for bilateral adrenalectomy if their metastatic disease first became evident when they were postmenopausal Instances of tumor regression, however have been reported in such women following adrenalectomy

Hypophysectomy

Since the pituitary plays such a pivotal role in the normal elaboration of steroid hormones and because certain pituitary hormones have long been suspect of influencing the growth of neoplasms directly the effect of total ablation of pituitary function upon the growth of established breast cancer is under cautious investigation in several clinical laboratories. Although the endocrine control of the hypophysectomized patient generally is somewhat easier than that of the adrenalectomized individual considerable technical difficulty has been encountered in effecting a complete ablation of hypophyseal function It has been adequately demonstrated that external irradiation of the normal pituitary almost never results in more than a temporary depression in glandular function It has also been found difficult to completely remove all of the functional gland by surgical extirpation, although techniques have recently been employed which seem to increase the probability of accomplishing this end result. Even more so than in the case of bilateral adrenalectomy it is at the present time impossible to evaluate the over all usefulness of hypophysectomy in the control of advanced breast cancer Suffice it here to say that several instances of tumor regression have been noted following this operation but several years of careful investigation are to be anticipated before a realistic evaluation of the procedure will be forthcoming

Cortisone Therapy

Objective and subjective improvement has also been reported in patients with metastatic breast cancer following the administration of cortisone Improvement has been noted following the daily administration of cortisone acetate in doses of from 50 to 75 mg orally, and since this dose is of the general order of magnitude employed in the control of the adrenalectomized patient the possibility exists that the improvement noted in some cases following adrenalectomy may be due to maintenance cortisone therapy However it is the belief of those with the most experience in following such patients that the degree of remission induced by the administration of physiological' doses of cortisone alone is considerably less than that seen following adrenalectomy Very large doses of cortisone have also been tested for tumor suppression effects and remissions have been noted in previously castrated patients who were given from 200 to 300 mg of cortisone acetate daily by mouth However in the small series of cases reported so far the induced remissions were short lived the longest lasting for only three months With the use of cortisone

in advanced breast cancer the usual precautions must be taken to supplement the patient's potassium intake and the general undesirable side effects of this hormone carefully watched for

The Place of the Endocrine Therapies in the Palliative Treatment of Patients with Advanced Breast Cancer

Now that a certain amount of consideration has been given to the specific responses that can be expected when various endocrine alterations are employed, some consideration should be given to where in the management of patients with advanced breast cancer each form of therapy can best be employed so as to afford maximal palliation Since all forms of endocrine therapy are associated with unpleasant side effects to various degrees, it is best, with few exceptions, to restrict their use to situations where their tumor suppressing effectiveness can be evaluated upon lesions not being treated simultaneously by other modalities Furthermore, as breast cancer tends to metastasize widely throughout the body, the generalized tumor repressant effects of endocrine alterations, when achieved, are very much to be desired Therefore, when therapy by these modalities is indicated, a sufficient trial period of treatment should be given before the particular regimen is abandoned as being ineffective In general, two to three months of treatment is required before a definitive evaluation of the procedure can be made If definite and unmistakable progression of the disease occurs during the first two months of treatment, continuing the therapy for longer periods offers little hope of effecting an objective improvement of the disease However, in instances where the disease remains stationary during the initial periods of observation, treatment should be continued, by all means, for in such cases objective improvement occurring several months after the initiation of treatment can be expected in a fair number of patients In spite of the slowness with which tumor regressions may occur following the administration of hormones, patients must be followed closely during the initial phases of treatment so that instances of acceleration of the disease process may be detected as early as possible and the few dangerous side effects that may occur as the result of therapy may be recognized and dealt with appropriately

In the over-all management of a case of advanced breast cancer, it is seldom a matter of deciding whether X-ray therapy or hormonal procedures should be employed exclusively, but rather which method can be best used when and for which particular lesions in order that the patient may be afforded the most desirable palliative relief There is no question but that X-ray therapy is considerably more effective in the treatment of osteolytic lesions of the skeleton than are our present endocrinological methods It is, therefore, obvious that radiation therapy is the treatment of choice in cases with relatively localized involvement of the skeleton, while endocrine procedures should be held in reserve until such time as the disease becomes widely manifested The only instance in which it seems advisable to combine endocrinological alteration with X-ray therapy for localized disease is in the case of the pre-menopausal woman in whom the local metastases involve the lower lumbar spine or certain areas of the pelvis so that during the administration of X-ray therapy considerable amounts of irradiation are necessarily delivered to the ovarian areas In such instances it would seem realistic to alter the X-ray therapy so that adequate irradiation is delivered to the ovaries to interrupt effectively ovarian function It is also evident that it is the metastatic deposits located in the major weight-

bearing areas of the skeleton that pose the greatest immediate threat to the patient's life and comfort It therefore, seems reasonable to treat such involvement by means of irradiation even in cases where the disease is widespread and endocrinological procedures are to be employed in an attempt to improve the generalized disseminated disease

As radiotherapy is also an effective method for treating recurrent and metastatic disease involving the superficial soft tissues of the body, its use is generally to be preferred, where feasible as the initial therapy for such lesions This is particularly so where the only evidence of disease is localized and restricted to the area originally encompassed by the primary surgical attack upon the disease Since breast cancer characteristically metastasizes widely it is a frequent experience to have new soft tissue lesions appear soon after the initial area of metastatic involvement has been successfully treated by means of radiotherapy Because the response of soft tissue lesions to estrogen therapy is a general one, we prefer to use this latter therapy as the initial treatment for women five or more *years past their menopause who show any* degree of superficial soft tissue involvement except where the involvement is very localized and limited to the area of the primary operation. If estrogen therapy fails as the initial form of treatment X ray therapy is then employed secondarily in those cases in which the involvement is not too extensive

With these general considerations in mind the following sequence of endocrine therapies is suggested for patients with advanced, recurrent or metastatic disease

Pre-menopausal Women

The induction of an artificial menopause is the initial endocrine procedure of choice since it results in the greater number of objective regressions and is generally associated with the least morbidity There is no indication that the concomitant use of androgenic steroids improves in any way the remissions induced by the interruption of ovarian function however where this procedure fails to benefit the patient or when tumor growth reappears after an induced regression a course of androgen therapy is indicated If tumor regression is obtained by this latter means, treatment should be continued until regrowth of the tumor becomes evident but then the hormone should be discontinued for in some instances improvement will follow this discontinuance

Recently Post menopausal Women (Less Than Five Years Post menopausal)

The initial endocrinological alteration of choice in this group of patients is the administration of androgenic hormone Should this therapy prove ineffective oöphorectomy may improve the situation in a relatively small number of cases particularly if the last menstrual flow has occurred within the previous two years Estrogen therapy may be tried only with the greatest of caution in cases that fail to respond to androgenic treatment where the menopause was artificially induced or where the natural cessation of menses occurred more than three years previously

Women Five or More Years Past the Menopause

In this group of patients, estrogen therapy is almost always the initial hormone therapy of choice The only exception may be the patient who is in severe pain as the result of skeletal involvement where the striking subjective effect so frequently obtained with the use of androgens may make them the preferential therapy In those cases that do not respond favorably to estrogen therapy androgens should of course be tried In those patients who respond favorably to

the initial estrogen treatment but in whom the tumor begins to regrow in spite of continued therapy, the treatment of choice is simply to discontinue administration of the estrogen If a second regression does not occur after a period of from one to two months, androgen therapy is indicated, for some very favorable results will be seen with its use

Males

Castration regardless of the age of the patient is the initial therapy of choice The administration of estrogens should be tried in those cases that do not respond to castration and in instances where regrowth of the tumor has again become evident (see Chapter XX)

The newer methods of altering patients endocrinologically have not been considered in this resumé, and as more experience with certain of them is gained, the above outline will probably require extension and revision It is also evident that situations probably will arise during the course of the management of any given patient in which the judicious use of irradiation will be most beneficial

In spite of considerable investigation into the effects of hormone alteration upon advanced breast cancer, no carefully controlled studies to indicate how much, if indeed any at all, additional useful life has been afforded patients with incurable breast cancer through the use of endocrine procedures It is very evident that in certain instances not only the patient's useful life, but also her actual life, have been significantly prolonged by the use of these measures, but it is also evident that in a relatively smaller number of cases life has been shortened by attempts at therapy Recently, efforts have been made to evaluate the contribution of hormone therapy to the palliative treatment of patients with advanced breast cancer, and although none of these data are without significant shortcomings, they do suggest that on the average several months can be added to the life of the patient with advanced breast cancer through the use of these modalities

Illustrative Cases

Case 1

Mrs E W was a 42-year-old woman who first sought medical aid because of severe pain in the back which radiated down the posterior aspects of both legs On examination a mass measuring approximately 4 cm in its greatest diameter was found in her right breast, and roentgenograms demonstrated a destructive lesion involving the second lumbar vertebra and numerous lytic lesions throughout the right hemipelvis as shown in fig 129 Since she was having menses at regular intervals, her initial therapy consisted of irradiation to the lumbar spine area with an alteration in the ports of administration so that adequate irradiation was delivered to the ovaries to inhibit function No therapy, other than the interruption of ovarian function, was directed toward the right breast or the right hemipelvis The mass in the right breast decreased gradually in size, and seven months later was no longer palpable Serial roentgenograms showed healing of the right hemipelvis and fig 130 shows the radiographic appearance of the pelvis seven months after ovarian irradiation This symptom-free remission was maintained for approximately 12 months Reactivation of the pelvic lesions then became evident, and the area was irradiated, but the patient's situation deteriorated rather rapidly Although a course of androgen therapy was recommended, because of her home situation she preferred to be admitted to an institution for terminal care where she expired three months later

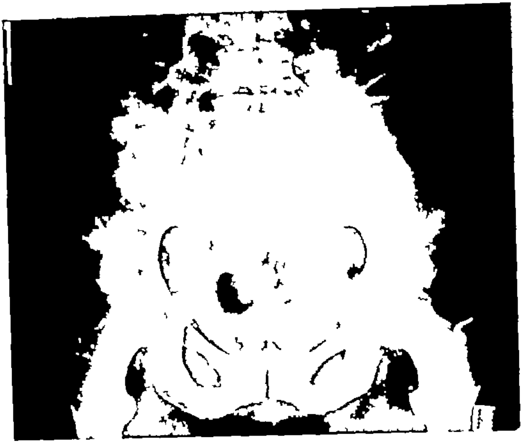

Fig 129

Fig 130

Figs 129 and 130 Illustrations in Case 1 showing the healing of osteolytic lesions in the right hemi-pelvis following ovarian irradiation in a 42 year-old woman

Case 2

Mr P G was a 68-year-old white male who first came to the tumor clinic because of back pain He had a small hard mass deep to the left nipple which he thought had been present for about a year Biopsy proved this to be a primary carcinoma of the breast He had numerous small subcutaneous nodules over his upper thorax, and roentgenograms demonstrated numerous lytic lesions throughout his skeleton similar to the one in the left ninth rib illustrated in fig 131 His initial treatment consisted only of bilateral orchiectomy which was followed by relief of bone pain, healing of the osseous lesions and a considerable decrease in the size of all the soft tissue lesions including the primary tumor mass The roentgenogram reproduced in fig 132 was made 11 months after orchiectomy A month later his back pain returned and roentgenograms indicated reactivation of several of the osseous lesions including those in the lumbar spine X-ray therapy was directed toward the lumbar spine resulting in some relief of pain, and the patient was started on a course of estrogen therapy The disease progressed slowly during four months of estrogen treatment so that it was discontinued, and he was subjected to a bilateral adrenalectomy He seemed to get some relief of pain following this procedure, and the superficial lesions appeared to be decreasing slightly in size However, two months after this second surgical procedure he insisted upon returning to his home some distance from the clinic, and within four weeks he developed a pyelonephritis and died rather suddenly

Case 3

Miss B M was a 60-year-old woman who first presented herself in the tumor clinic with the large untreated carcinoma of the left breast shown in fig 133 The tumor mass was fixed to the chest wall, there were several hard fixed nodes in the left axilla and satellite skin nodules that are visible in the photograph No distant metastases were demonstrable although the patient stated that she had first noted a mass in the left breast approximately three years prior to her coming to the clinic As her last menstrual flow had occurred when she was 48 years of age, she was treated with diethylstilbestrol 15 mg per day by mouth which she tolerated very well A very rapid regression of all tumor deposits resulted, and after two months of treatment only an area of induration remained at the site of the primary lesion The photograph reproduced in fig 134 illustrates the situation at that time Pigmentation of the right nipple is evident as is considerable pigmentation of the skin throughout the area of primary involvement and of the axillae Several biopsies taken throughout the period of remission always revealed residual tumor, although the degree of clinical regression appeared to be fairly complete Thirteen months after the beginning of treatment she developed extensive metastases in the left hemipelvis resulting in a pathological fracture through the acetabulum At this time metastatic lesions were also evident in the calvarium and lumbar spine, and the area of the primary lesion appeared to be reactivating Estrogen therapy was discontinued, and a course of X-ray therapy, which resulted in considerable pain relief, was directed toward the left hemipelvis and lumbar spine In spite of this therapy she remained bedridden and was unable to return to the clinic until her death approximately one year later during which time she received only symptomatic therapy

Case 4

Miss E J was 63 years of age when she first came to the tumor clinic with a large untreated carcinoma completely replacing

Figs 131 and 132 Illustrations in Case 2 showing an osteolytic metastasis in the ninth rib of a male with advanced breast cancer Initial treatment consisted of bilateral orchiectomy Healing of rib 11 months after treatment

Fig 131

Fig 132

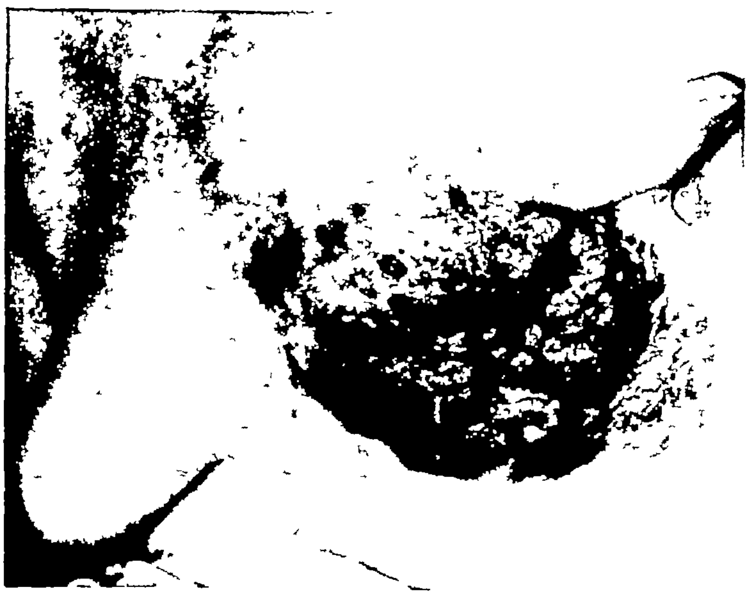

Fig 133

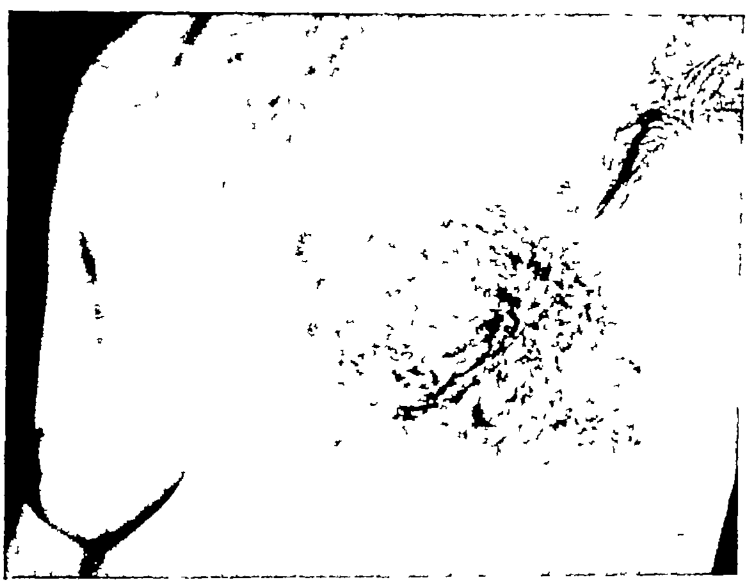

Fig 134

Figs 133 and 134 Illustrations in Case 3, showing primary tumor before and two months after estrogen therapy

her right breast which, she stated, she had first become aware of about three years previously It was fixed firmly to the chest wall, there were fixed axillary nodes present one of which had become ulcerated, and the patient was experiencing considerable low back pain which radiated down the posterior aspect of the right leg The roentgenogram reproduced in fig 135 demonstrated a destructive process involving the pedicles of the lower three lumbar vertebrae, but no other distant metastases were demonstrable Her last menstrual flow had occurred 15 years previously so that she was started on oral diethylstilbestrol 15 mg a day Within a month her back pain had almost completely disappeared, and her primary lesion was decreasing in size Serial roentgenograms made at intervals over the following months demonstrated healing of the lytic process with the development of sclerotic bone in the lumbar pedicles, and the primary tumor mass regressed to less than one third its original size The roentgenogram reproduced in Fig 136 was made 18 months after the institution of therapy Although in this

Figs 135 and 136 Illustrations in Case 4 showing the appearance of osteolytic lesions of the pedicles of the lower three lumbar vertebrae before and 18 months after estrogen therapy

Fig 135

Fig 136

patient the skeletal lesions responded very well to estrogen therapy, subsequent experience has indicated that this occurs relatively infrequently, and that it is better in such cases to administer X-ray therapy to the osseous lesions located in major weight bearing areas, and then to institute hormone therapy in an attempt to control the extensive soft tissue disease

Estrogen therapy was continued and the induced remission was maintained for three and a half years She then developed a severe right ophthalmoptosis, numerous lytic lesions appeared in the calvarium and the large lytic lesion shown in fig 137 developed in the region of the left sacroiliac joint At this time there was no evidence of reactivation of disease either in the lumbar pedicles or on the right chest wall After forty-three months of continuous administration, estrogen was discontinued, and no other treatment given The ophthalmoptosis improved greatly, all lesions in the calvarium decreased in size, and the left sacral lesion healed The roentgenogram reproduced in fig 138 was made five months after discontinuing estrogen administration The skeletal lesions remained improved, but, by the eighth month without therapy, multiple skin metastases appeared below the area of the primary lesion so that three months later estrogen was restarted This resulted in only

Fig 137

Fig 138

Figs 137 and 138 Illustrations in Case 4, showing the appearance of an osteolytic metastasis in the left sacroiliac region Five months after discontinuing estrogen therapy which had been given continuously for 43 months, the lesion of the left sacroiliac joint appeared sclerotic and healing well

questionable improvement in the superficial metastases so that after four months a course of androgen treatment was begun She experienced some nausea with this change in therapy, but with continuation of hormone therapy she experienced a real subjective improvement which was associated with a minor degree of regression of the superficial tumor deposits This improvement while on androgen therapy was maintained for six months. The disease again began to progress, and the patient expired 6.3 years after institution of hormone therapy having been able to carry on her household duties and to work in her garden for 5.5 years of this time

Case 5

Miss E C was 61 years of age when estrogen therapy was instituted in an effort to control the extensive spread of her breast cancer Thirteen years prior to this she had had a small carcinoma of the right breast removed locally, but because of enlargement of the supraclavicular nodes at that time radical surgery was not carried out, and she received X ray therapy to the right chest wall, axilla and supraclavicular area. She remained free of demonstrable disease for ten years, but during the next three years she developed superficial metastases in several areas which were treated by the implantation of radon seeds. During the three to four months prior to her referral to our clinic she had developed a dry cough had become severely dyspneic and unable to continue working, had developed numerous cutaneous nodules and had lost peripheral vision in her left eye The roentgenogram reproduced in fig 139 revealed extensive metastases of the lymphogenous type involving both lung fields, and ophthalmoscopic examination revealed a whitish nodule in the left retina Since she had had a bilateral oöphorectomy at the time of initial treatment 13 years before she was given diethyl stilbestrol 15 mg per day by mouth She tolerated this initial treatment well, the dyspnea gradually disappeared and her vision returned essentially to normal The roentgenogram reproduced in fig 140 was made four months after the institution of estrogen therapy The remission lasted for six months when evidence of regrowth of the cutaneous nodules appeared However neither the lung lesions nor the retinal lesion reactivated and the patient was able to continue working Estrogen was discontinued after nine months of continuous administration A year after the institution of estrogen therapy osetoblastic lesions were demonstrated in the lumbar spine and pelvis, and attempts were made to restart estrogen therapy The patient experienced considerable general malaise with this therapy and as she was experiencing no discomfort from her disease and the superficial lesions were progressing only very slowly, she preferred to discontinue treatment Nineteen months after initiation of estrogen therapy she developed a pleural effusion and evidence of reactivation of her pulmonary metastases was indicated radiologically and by the reappearance of dyspnea. A four month course of estrogen therapy resulted in improvement of her intrapulmonary disease and respiratory symptoms, but no resolution of the pleural effusion resulted and her skeletal lesions were unaffected She had experienced some general malaise during this course of therapy Estrogen was discontinued and androgen therapy started She was unable to tolerate this change in therapy experiencing severe muscular aching and weakness and refused to continue with it No further therapy was given, and she expired with abdominal involvement 32 months after beginning estrogen therapy Although she experienced moderate discomfort in the form of muscular aching during the last two periods of estrogen administration she had been able to return to her secretarial job shortly after beginning

FIG 139

FIG 140

FIGS 139 and 140 Illustrations in Case 5, showing lymphogenous type of bilateral pulmonary metastases Clearing of lower lung fields four months after beginning estrogen therapy

estrogen therapy and to continue working until two months before her death

Case 6

Mrs A M was a 65-year-old woman who came to the tumor clinic because of a mass that had been present in her left breast for approximately one year The mass measured 3 cm in its largest diameter, was fixed to the deeper layers of the skin but was freely movable over the chest wall There were two small satellite lesions on the skin of the

breast single small nodes were palpable in either axilla, and roentgenological examination revealed a small lytic lesion in the right pedicle of the fourth lumbar vertebra and another lesion in the left pubic ramus fig 141 Her serum calcium level was found to be 11 9 mg per cent As she was experiencing no pain referable to the small lesion in the lumbar spine and her last menstrual flow had occurred 15 years previously 15 mg of diethylstilbestrol per day by mouth was prescribed Although she experienced no particular nausea upon institution of therapy, within four weeks she developed severe nausea and anorexia, began to vomit and became somewhat lethargic Her serum calcium was found to be 18 7 mg per cent so that the hormone was immediately discon

Fig 141

Fig 142

Figs 141 and 142 Illustrations in Case 6 showing striking increase in the extent of osteolytic metastases after only one month of estrogen therapy

tinued, and she was hospitalized for supportive fluid therapy Roentgenograms revealed a striking increase in the number and size of the lytic lesions in the lumbar spine, pelvis and left femur (fig 142) although no change in the size of the soft tissue lesions had occurred During two weeks of hospitalization, the symptoms referable to hypercalcemia gradually remitted, and her serum calcium level declined to 10 8 mg per cent Her BUN, which had been 76 mg per cent shortly after admission, fell to 43 mg per cent, but the seriousness of this degree of impairment in renal function in conjunction with hypercalcemia was not appreciated Estrogen therapy was reinstituted, and the

Fig 143 A

Fig. 143 B

Fig 143

A Patient observed at the Johns Hopkins Hospital and considered "categorically inoperable" because of advanced and bilateral (confirmed by biopsy) breast cancer

B After one year of treatment consisting only of radiotherapy followed by testosterone proprionate 100 mg three times weekly There was no surgical procedure other than biopsy performed on this patient Despite the spectacular palliative response to this combined therapy, this patient ultimately died of liver metastases

FIGS 144 A and B A large solitary pulmonary metastasis in the right lower lung field which responded favorably to three months of estrogen (ethinyl estradiol) therapy

patient was discharged Two weeks later she was readmitted in a semicomatose condition having been vomiting persistently during the previous three or four days. Her serum calcium was found to be 19 0 mg per cent and her BUN had risen to 60 mg per cent The hormone was again discontinued and intravenous fluids including 2.5 per cent sodium citrate were administered Within a week her sensorium had cleared her serum calcium had declined to 17 6 mg per cent and her BUN to 34 mg per cent No further hormone therapy was attempted and she was again discharged Twelve days later she was re-hospitalized in a comatose condition, her serum calcium was 22.3 mg per cent and her BUN 135 mg per cent In spite of intravenous fluid therapy including sodium cit

FIGS 145 A and B An osteolytic lesion in the fourth rib which healed and remained healed for two years after ten months of testosterone therapy Patient subsequently developed cancer in the remaining breast

rate, she failed to improve and expired nine days later. Permission for an autopsy could not be obtained.

Possible Mechanisms by which Endocrine Alterations May Influence Tumor Growth

Certainly at present it is impossible to give a satisfactory explanation for all of the responses of established breast cancer which are observed following various therapeutic alterations in the "endocrine environment." The mere fact, however, that regressive changes do occur in cancer of the breast and prostate following withdrawal of certain of the hormones being produced normally by the body and also following the administration of hormones in near-physiologic quantities, is in itself of considerable theoretical importance to our concepts concerning malignant neoplasia. The time-honored dictum that cancer represents an autonomous growth of cells over which the body exerts no control seems to be belied by these observations. In its place a newer concept has arisen that certain cancers, although they exhibit all the anatomic criteria of malignancy, still require some definite stimulus supplied by the host in order for them to maintain the biological characteristics of malignant neoplasia. In this sense, the growth of these cancers is still being controlled by bodily mechanisms, and they are, therefore, referred to as being "dependent" cancers. Furthermore, the fact that certain of the responses of established breast cancer do not appear to be readily explainable on such a basis and yet we believe that hormones exert their effects through established and functional body mechanisms would suggest that the host does retain a certain degree of positive control over the growth of these tumors. In such instances the administration of hormones may act to strengthen these mechanisms and thus temporarily to bring the growth of the cancer more completely under control.

The next logical question would seem to be "Can the growth of such dependent cancers be permanently controlled either by removing these growth stimulants or by augmenting some functioning, though inadequate, controlling mechanism?" This question cannot be completely answered at present. As far as the known endocrine alterations are concerned, regrowth of the effected neoplasm seems always to occur, but the question still remains whether this regrowth occurs as the result of an increasing autonomy on the part of the tumor or whether it is due to some compensatory change on the part of the host which negates the original endocrine alteration. It seems most probable that both situations occur. As far as the ultimate definitive control of these dependent cancers by endocrinologic means is concerned, the results of investigations employing certain experimentally produced animal tumors as well as certain human tumors transplanted to the eyes of experimental animals would seem to paint a rather pessimistic picture. The sequence of events usually observed under these experimental conditions is that, although the tumors are controllable during early transfer generations, as transplantation is continued they appear to become more and more autonomous until finally they are relatively uneffected by the previously effective endocrine alterations. These experimental results appear strikingly similar to the experience in human beings where in any given patient all effective means of endocrine control eventually fail.

It seems most probable that in the case of oophorectomy one is depriving the cancer of the specific growth stimulating effects of the estrogenic hormones. Since in only about a third of the cases this procedure is followed by a demonstrable decrease in the size of the

tumor deposits it has been postulated that there are two types of breast cancer in women one estrogen dependent, the other not. It would seem a bit more realistic to postulate that breast cancers occur with varying degrees of dependency as far as estrogenic stimulation is concerned Thus oöphorectomy in patients with tumors that are entirely estrogenically autonomous results in no suppression of tumor growth in others who have breast cancers that have retained a slight degree of estrogen dependence only a slowing of the growth rate would be seen and as patients with tumors retaining greater and greater degrees of dependency are treated more and more striking degrees of tumor regressions are noted Regrowth of the tumor might then be due to the extragonadal production of a significant amount of estrogen as suggested by a favorable response to adrenalectomy but it also seems probable that the tumors tend to become more autonomous since not all instances of reactivation respond favorably to adrenalectomy, and eventually the tumors appear to lose all responsiveness to endocrine alteration

The administration of androgens at the dosage levels found to be effective in the suppression of tumor growth may also exert its effect, at least partially by decreasing the level of circulating estrogens This would be effected through a suppression of pituitary gonadotropins which govern the output of the estrogens by the gonads and possibly also by extragonadal tissues. Under certain specific experimental conditions it can also be shown that androgenic hormones are capable of inhibiting some of the reactions elicited by the estrogens It is possible therefore, that the androgens may both reduce the production of estrogenic hormones by the body and also inhibit the end organ response to those that are circulating However the fact that androgens are as effective in causing tumor regressions in older, post menopausal women as they are in young women during active menstrual life in which the production of estrogen would appear to be the higher, would seem to be evidence against the argument that their primary action is to reduce estrogenic stimulation Androgens are known to exert a considerable effect upon protein anabolism and calcium metabolism and to influence pituitary function other than the elaboration of gonadotropin in the non tumorous individual so that it seems possible that they may have a tumor suppressing action entirely separate from any anti-estrogenic effect. The observation that when tumor regrowth occurs following an initial period of regression discontinuance of androgen therapy sometimes is followed by improvement in the tumor is difficult to fit into any of the above theories of the mode of action of these compounds It has been suggested that this might indicate that the tumor has become androgen dependent during the period of therapy, but this concept is hard to accept in the absence of any specific data to support it In this connection it should be remembered that the administration of testosterone increases the urinary excretion of estrogenically active compounds and that these may be exerting some effect either stimulative or inhibitory, upon the tumor

As yet there is no reasonable thesis supported by experimental or clinical data to explain the regressive changes seen in advanced breast cancer in elderly women following the administration of estrogens That these compounds may stimulate the growth rate of breast cancer in young women has been all too frequently demonstrated Why then tumor regression should occur in the older post menopausal woman remains an enigma. It has been suggested that in the dosages used the estrogens may actually stunt mammary gland growth as is the

case in experimental animals when massive estrogen therapy is given and that such an effect might be the basis for their tumor suppressive action. However, it has been demonstrated recently that during the course of estrogen therapy for breast cancer the normal epithelium of the breast frequently is intensively stimulated resulting in considerable amounts of proliferation at the same time that the neoplastic breast tissue is undergoing regressive changes. It is possible, of course, that the administration of relatively large doses of estrogen, and of androgens and corticoids as well, may exert a tumor-suppressive effect through the suppression of some specific pituitary function. At the present time, however, there is no experimental or clinical evidence that points strongly to this mode of action of the steroid hormones except, of course, the fact that tumor regressions have been noted following hypophysectomy.

In any consideration of the mode of action of the estrogenic hormones, some attention must be given to the stroma since tumor deposits in the soft tissues of the body regress considerably more frequently than do those in the bony skeleton. Also, in patients with metastases in both types of tissue, regression of the soft tissue lesions may be observed in the presence of progression of the lesions involving the bony skeleton. That the stroma plays some important role in estrogen induced regressions is further suggested by the observations that recurrent superficial disease is less likely to respond favorably when it occurs in areas that have previously been irradiated, and certainly irradiation profoundly effects the connective tissues. It has been suggested that estrogen administration may cause a proliferation of the fibroblastic stroma of the tumor, and this stroma may effectively "choke off" the tumor cells. It is true that as the tumor cells decrease in number there is a relative increase in the fibrous stroma, but we have been unable to find evidence that active fibroplasia occurs during the active phase of tumor regression. In fact, in following a group of tumors through active regression by means of serial biopsies, we have not only failed to see evidence of active fibroplasia, but in two instances in which the tumors showed active stroma proliferation prior to therapy all evidence of fibroblastic activity disappeared as the tumors began to regress. Thus, although the supporting tissue of the tumor appears to be of considerable import, it does not appear to exert its influence through the induction of active fibroplasia.

The greater tendency for tumor regression to occur in lesions involving the soft tissues of the body, also make one wonder if under these special conditions the administration of estrogens may not augment some natural resistance that the host has to the progressive growth of breast cancer. Such an hypothesis might also be employed to explain the secondary regressions noted following discontinuance of therapy as well as the differences noted in tumor response depending upon the "physiological" age of the patient. If one assumes that these "estrogen-dependent resistance factors" deteriorate only slowly in the absence of estrogen and that both the tumor cells and the resistance factors are stimulated by treatment, tumor regression would occur in those instances in which the increase in body resistance significantly exceeded the stimulative effects on the tumor. When regrowth occurs and estrogen is withdrawn, the resistance factors remain effective for some time while the stimulative effect upon the tumor disappears more quickly and a second regression results. In pre-menopausal women, the resistance factors may be considered to be essentially maximal already, and the addition of more estrogen usually results in no advantage to this host-tumor relationship or may even

result in an increase in the rate of tumor growth Such a scheme is of course, highly speculative for as yet the nature and even the very existence of such natural resistance factors has not even been experimentally demonstrated

It seems obvious from this brief considera tion that at the present time it would appear best to admit that there is no satisfactory explanation for the effectiveness of estrogen therapy in the management of advanced breast cancer and that the use of the regimen remains on an *entirely empirical basis.* The same statement may be equally valid in the case of androgen and cortisone therapy and certainly is true of the regressive changes so frequently seen following castration in the male. In this latter instance it might be assumed that the testes produce sufficient estrogens that their removal acts much in the same manner as the removal of ovaries *in the female However the fact that the* administration of estrogen even to intact males may result in a tumor regression which can be continued and even augmented by discontinuing the estrogen and castrat ing the patient makes this explanation *somewhat* untenable

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CHAPTER XVII

Breast Cancer and Pregnancy or Lactation

The coexistence of breast cancer and pregnancy is fraught with grave peril, encompassing as it does the cares, fears and hopes of today as well as of tomorrow The seriousness of the situation is ' easy to see but hard to foresee." Although the future should be planned by the present, yet in these complex problems requiring delicate decisions we are often forced to rely upon unpredictable and intangible clinical experience and how this audit stands, no one knows, save Heaven.' In the matter of prognosis, for example there is no divine guidance for the advice to women recently operated upon for breast cancer who are anxious to bear children Current clinical opinion concerning breast cancer and pregnancy is beset with all too many conflicting points of view

Incidence

The coincidence of breast cancer and pregnancy is a relatively rare but exceedingly important complication Finn (7) has reported that 62,561 patients were observed during pregnancy at the New York Lying In Hospital between 1932 and 1950 and during this time 46 of these women were found to have breast cancer—an incidence of one case of breast cancer for every 1,360 pregnancies White (25) reported the number of patients with carcinoma of the breast observed in three large obstetrical services. In 123,884 pregnancies there were only 13 patients with breast cancer Since almost 75 per cent of the patients develop breast cancer after the age of reproduction, it is not surprising to find so small a ratio and so narrow a margin of overlap between pregnancy and breast cancer The prevalence of breast cancer is highest between the age range of 45 to 60 whereas the birth rate in the United States is highest between the age range of 20 to 25 In European countries the birth rate appears to reach a peak between the age range of 25 to 30

Harrington (13) in a long term survey of 4,628 patients with breast cancer observed at the Mayo Clinic found 92 women who were either pregnant or lactating at the time their tumor was discovered Thus, pregnancy or lactation occurring simultaneously with breast cancer can be anticipated in about two per cent of all women with mammary malignancy A comprehensive review of the literature by Westberg (24) indicates that this incidence may vary slightly in accord with individual experience Pregnancy alone may occur as a complication of breast cancer in between 0.5 and 3 6 per cent of the cancer patients, whereas lactation alone may occur as a complication of breast cancer in between 1 0 and 4 6 per cent of the patients.

The Relationship Between Breast Cancer and Pregnancy or Lactation

When breast cancer occurs during pregnancy the rapidity of malignant growth appears to be accelerated and the duration

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Incidence

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Harrington (13), in a long term survey of 4 628 patients with breast cancer observed at the Mayo Clinic found 92 women who were either pregnant or lactating at the time their tumor was discovered Thus, pregnancy or lactation occurring simultaneously with breast cancer can be anticipated in about two per cent of all women with mammary malignancy A comprehensive review of the literature by Westberg (24) indicates that this incidence may vary slightly in accord with individual experience Pregnancy alone may occur as a complication of breast cancer in between 0 5 and 3 6 per cent of the cancer patients, whereas lactation alone may occur as a complication of breast cancer in between 1 0 and 4 6 per cent of the patients.

The Relationship Between Breast Cancer and Pregnancy or Lactation

When breast cancer occurs during pregnancy the rapidity of malignant growth appears to be accelerated and the duration

of survival shortened The sinister influence which pregnancy exerts on breast cancer is probably the result of several factors

1 Pregnant women who develop breast cancer are of a younger age range when the prognosis is considered to be generally less favorable (17, 19, 24)

2 The physiologic engorgement and hypertrophy of the breast associated with pregnancy may mask the presence of a deep-seated small or early tumor, thus delaying the diagnosis until the disease is more advanced

3 The increase in breast vascularity during pregnancy favors greater growth and opportunity for metastatic dissemination of breast cancer as well as increased local invasiveness

4 Natural and synthetic estrogens have been shown to act as a physiologic stimulus to normal breast tissue During pregnancy the level of estrogens is markedly elevated, and although the exact mode of action is by no means clear, target-organ tumors apparently respond adversely to this type of sex steroid stimulation (21) Advanced or metastatic breast cancer in a premenopausal patient can be favorably affected by castration and exacerbated by the administration of estrogens (refer to Chapter XVI) In my experience, women with recurrent or metastatic breast cancer who unfortunately become pregnant deteriorate clinically due to their malignancy at a precipitous rate

Experimental Studies

The endocrine control of the breast is unusually complex for what anatomically is a relatively simple end organ Hormones of the ovary, pituitary and adrenal glands all appear to be directly involved in either its growth or function (refer to Chapter III) Among laboratory animals mammary cancer is almost entirely found in females, and in some strains of mice it occurs with marked frequency in females that have been pregnant Removal of the ovaries will prevent mammary cancer in mice except in instances of adrenal tumors

A large number of experiments confirming the original work of Lacassagne (15) have clearly demonstrated the influence of estrogens on tumorigenesis in mice The administration of adequate amounts of estrogens has been followed by mammary cancer in suitable strains of mice The morphologic changes in the mammary glands generally parallel those observed in multiparous females except that more cystic distention and many more hyperplastic nodules appear In the opinion of Gardner (10), however, estrogens do no more than do the intrinsic hormones of multiparous females in their contribution to mammary carcinogenesis in mice "Mammary tumors in mice, develop in hormonal environments that do not seem to deviate from those compatible with normal reproductive functions "

Foulds (8) has described mammary tumors in mice which appear only during pregnancy and which regress between pregnancies Eventually, however, these experimental tumors become "autonomous" and continue to grow progressively It is generally believed that mammary tumors in experimental animals may be caused by several different factors (see Chapter IV) However, the role of the sex steroids is necessary initially for the development of the mammary glands—the soil in which these tumors arise Furthermore, some of the "virus induced" tumors are hormone dependent for continued growth The hormones which are produced in excess of normal during pregnancy may be considered to affect seriously the environment of an experimental mammary tumor and adversely affect or stimulate malignancy Such growth stimulating hormones as estrogens,

progesterone and the gonadotropins act normally in a cyclic fashion upon the mammary gland Although the factors associated with the origin of mammary tumors may not be the same quantitatively or qualitatively as those associated with enhancement of their growth yet the abnormal hormone environment of pregnancy can be considered a factor in altering the activity of mammary tumors in mice

The sex steroids by classical definition must be present in the circulating blood in biologically effective concentrations The difficulties of measuring such steroid hormones when present in amounts so minute as to be almost undetectable, as well as the fact that they may appear only periodically and then perhaps in active or inactive forms, render the reliability of this complex estimation a rather uncertain procedure The critical measurement of such small amounts of a sex steroid even by a fractional chromatographic-adsorption technique requires an expensive and time-consuming laboratory procedure which is so elaborate as to make it impractical and scarcely useful for routine use. Such delicate yardsticks are, however urgently needed for the acquisition of precise and vital information concerning the steroid level in body fluids and tissues

Gross biologic tests, performed both during the pregnant and nonpregnant states, indicate that the selective action of estrogens is rather specific for the endometrium and the epithelium of the breast prostate and mucous membranes of the body This action is due either to the selective sensitivity or the selective absorption by these tissues There is, however a wide gradation of responsiveness which is normally present during pregnancy and at other times as well This is true not only between one breast and another but between different portions of the same breast

In an attempt to understand the mechanism of action of estrogens in breast cancer, Lewison Levi, Jones, Jones, Jr and Silberstein (16) administered radioactive sodium estrone sulfate labeled with S^{35} to seven patients with advanced breast cancer The radioactivity present in the blood urine and feces, as well as in the normal and cancer bearing breast and other tissues, was determined From this preliminary investigation it was concluded that when tracer amounts of an S^{35} labeled estrone sulfate were administered to patients with advanced breast cancer, the concentration of radioactivity was highest in the tissue of breast cancer The second order of magnitude for the concentration of radioactivity appeared to be within the epithelium of the female genital tract Davis and his co-workers (6) were unable to find similar results in animals However, there are several studies which indicate that the sex steroids have a direct effect upon primary breast cancer and its metastases

Clinical Studies

In a comprehensive survey of 4,628 cases of breast cancer treated at the Mayo Clinic, Harrington found that 92 women were either pregnant or lactating at the time they discovered their tumor The average age of this group of women was 36 6 years and an unusually high percentage (84.8 per cent) of these patients had metastases to the axillary nodes at the time of operation By comparison with the entire Mayo Clinic series of patients with breast cancer only 63 8 per cent had axillary metastases at the time of operation

The survival rates in this study of patients in whom breast cancer occurred simultaneously with pregnancy or lactation are shown in table 72

It is evident from this Mayo Clinic study that when breast cancer occurs in the course of pregnancy or lactation metastases

TABLE 72

Ninety-Two Patients with Breast Cancer in Whom the Tumor Was Present in Course of Pregnancy or Lactation

Seventy-Eight Patients (84 8 per cent) With Axillary Metastases and Fourteen Patients (15 2 per cent) without Axillary Metastases

Group	Percentage of Patients Traced* Who Lived More Than Indicated Years after Operation			
	3 yrs	5 yrs	10 yrs	15 yrs
Total	23 9	14 5	8 7	4 5
With axillary metastases	17 3	5 7	3 4	0 0
Without axillary metastases	61 5	61 5	40 0	25 0

* The three year percentage is based on patients traced three or more years after operation, the five year percentage on patients traced five years or more after operation, etc (S W Harrington (13))

to the axillary nodes are frequent and the over-all results as determined by survival are generally poor Harrington noted the effect of major breast surgery upon subsequent delivery in a total of 11 women Seven women were delivered normally at full term, and four women had early miscarriages presumably as the result of mastectomy

A special survey was undertaken by Harrington to determine the survival of women who had been operated upon for breast cancer and who subsequently became pregnant The average age of this group of 55 women was 34 2 years There were 27 women who had a single livebirth following mastectomy, ten women who had two livebirths, two women who had three livebirths, three women who had a single stillbirth, 12 women who had a single miscarriage and one woman who had two miscarriages The shortest interval between the breast operation and the birth of a live baby at full term was about 11.5 months, and the longest interval was about 12.5 years In 22 of the 39 women having livebirths, parturition occurred during the first three years postoperatively

It must be clearly understood, of course, that this special series was of necessity a highly selective group of cases Harrington points out that women with "more serious types of malignant disease do not survive long enough to become pregnant subsequently " It is also to be noted that the incidence of axillary metastases (a prognostic index of some import) in this group of women was only 45 5 per cent as compared with 63 8 per cent for the entire series The survival rates for this group of 55 women who became pregnant after operation for breast cancer are shown in table 73

Harrington concludes from this survival study of "traced" patients (only two-thirds of the total number could be "traced" at ten years) that, "it is difficult, and may be hazardous, to draw any definite conclusions from this study other than what has been stated above, namely, that it is possible for patients to bear children following radical amputation of the breast and to live for many years without recurrence " Although the survival results in those women who became pregnant subsequent to operation for breast cancer were "far better than it was expected they would be, we shall continue to advise young women who are in the child-bearing period of life not to have subsequent pregnancies "

In a careful review of the influence of pregnancy on cancer of the breast, Brooks and Proffitt (4) point out that it has been their practice *not* to urge patients to avoid pregnancy postoperatively, "if we had reasonable grounds for a belief that all tumor cells were removed " Sterilization or birth control measures were recommended to women for whom the prognosis was less favorable "We have attempted to give the

patient an understanding of the possible deleterious effect of pregnancy on existing cancer of the breast in order that she might have an opportunity of herself choosing between living a year longer with no child or a year less and realize a necessary fundamental longing'

In six patients studied Brooks and Proffitt found breast cancer associated with pregnancy in three and breast cancer associated with lactation in three, in five additional patients pregnancy occurred following radical mastectomy Of the six patients in whom breast cancer coexisted with pregnancy or lactation, all had gross evidence of axillary metastases and five out of six died within two years after operation. Relatively short term observation of the five patients becoming pregnant after radical mastectomy revealed only one death in a patient with extensive axillary metastases There were no instances in this small group of women followed postoperatively for less than seven years of a second primary or metastatic breast cancer in the remaining breast Trout (23) in an early report noted that cancer developed in the remaining breast in 15 out of 17 women who became pregnant after radical mastectomy However Brooks and Proffitt found no clinical evidence to support the idea that pregnancy could be considered an inciting agent in the etiology of breast cancer in the remaining breast However these authors believed that pregnancy exerted a decidedly deleterious influence on a coexisting breast cancer by increasing its rate of growth and favoring its rapid and widespread dissemination

Whether or not a patient during the child bearing age, operated upon for cancer of the breast is to be advised against pregnancy told it is not contraindicated or a discussion of the subject entirely omitted is solely an affair of the surgeon and the patient and each instance should have individual consideration based entirely on the surgeon's judgment as to the probability of the complete removal of all the neoplasm and the patient's ability to understand and choose the amount of risk involved for diminishing an already short life expectancy if all the tumor is not removed With residual cancer the life expectancy, already short, would be further shortened by pregnancy but one can well imagine that the sum total of happiness of a childless woman living for an additional four years might be less than her living for only one year if this one year were composed of nine months of anticipation and three months was realization of having accomplished her most primitive obligation for the survival of the race'

The experience of Geschickter (9) com-

TABLE 73

Survival Rates in 55 Patients Who Became Pregnant After Operation

Group	Lived 3 or More Years: Patients traced	Lived 3 or More Years: Patients (survivors)	Lived 3 or More Years: Per cent of traced patients	Lived 5 or More Years: Patients traced	Lived 5 or More Years: Patients (survivors)	Lived 5 or More Years: Per cent of traced patients
Totals	55	52	94.5	53	42	79.2
With axillary metastases	25	22	88.0	23	13	56.5
Without axillary metastases	30	30	100.0	30	29	96.7
	Lived 10 or More Years			**Lived 15 or More Years**		
Totals	37	28	75.7	21	15	71.4
With axillary metastases	12	6	50.0	5	3	60.0
Without axillary metastases	25	22	88.0	16	12	75.0

(After S W Harrington (13))

cides with most other clinical investigators In a study of 15 women with breast cancer occurring during pregnancy, axillary metastases were present in every patient and death followed operation in less than three years in 13 out of 15 One patient was lost to follow-up and one patient was alive and well almost two years postoperatively Four women developed breast cancer shortly after having had a miscarriage Two of these women died 12 and 19 months following radical mastectomy, and two were alive and well six and seven years after surgery Geschickter states that since the prognosis is more favorable following spontaneous abortion than if the pregnancy were to continue without interruption, "Therapeutic abortion is indicated in the first two-thirds of pregnancy if the disease is not hopelessly extensive at the time"

Thirty-seven patients with breast cancer were operated upon during or shortly after lactation The five year survival of these women was 21 per cent (eight patients), which indicates a considerably better prognosis than for those patients in whom breast cancer occurred during pregnancy However, when compared with the five year survival of all patients with breast cancer uncomplicated by pregnancy or lactation, the prognosis can hardly be considered satisfactory

Although Bromeis (3) and Mankin (18) have suggested that in studies of prognosis it is incorrect to consider pregnancy and lactation in one clinical category, yet in the comprehensive monograph of Westberg (24), he finds statistical justification for considering these two closely related conditions under a single category from the point of view of survival In addition to an exhaustive review of the literature, Westberg collected 4,747 cases of breast cancer treated at various hospitals throughout Sweden from 1921 to 1943 This clinical material consisted of 3,286 women who were treated at the Radiumhemmet in Stockholm, 528 women treated in southern Sweden and 709 women treated in the provinces of Norrland There were in addition 90 women in whom breast cancer occurred during pregnancy, 68 women in whom breast cancer occurred during lactation and 47 women who became pregnant after treatment for breast cancer

Westberg found the prognosis to be less favorable in those patients in whom breast cancer occurred during pregnancy or lactation However, he noted that the delay in diagnosis in these patients averaged two months longer than the remainder of the group It is indeed likely and quite natural for pregnant and lactating women to misinterpret the early signs and symptoms of breast cancer Operative treatment also was frequently found to be postponed either due to doctor or patient delay This added to the poor prognosis and may account for the exceptionally high incidence of axillary and distant metastases in this group In an age for age comparison, Westberg found the prognosis to be only slightly less favorable if one considers only women less than 35 years of age with breast cancer alone as compared with all women with breast cancer coincident with pregnancy Nothing could be found to recommend a postponement of surgery for women in whom breast cancer coexisted with pregnancy or lactation "On the contrary, in view of the rapid development of the tumor to a higher stage it must be considered unsuitable to delay the surgical treatment even for but a week or two" Spontaneous abortion following mastectomy occurred in five per cent of the patients Based upon a very small number of cases, no definite conclusions could be drawn regarding the possible justification of arresting pregnancy while treating breast malignancy "Nothing has

been found to bear out the opinion that induced abortion should improve the prognosis. Patients who subsequently became pregnant after breast surgery were probably a selected group and statistically their death risk appeared to be no greater than for breast cancer patients in general

Smith (22) is one of the few authors to consider that the interruption of pregnancy in a woman with breast cancer is actually harmful In support of this unique opinion he noted a decreased tempo of tumor growth during pregnancy and an acceleration following delivery or abortion. However, these conclusions based upon only 54 cases must be accepted with great reservation

Hochman and Schreiber (14) indicate that although pregnancy may induce the growth of breast cancer in experimental animals, it does not necessarily prove that pregnancy enhances the malignancy of an existing tumor Clinical evidence is conflicting in that women with a low fertility rate and unmarried women have a higher than average incidence of cancer These investigators studied the survival results in 20 patients in whom breast cancer occurred in conjunction with pregnancy Despite the small number of patients the five year survival rate (40 per cent) corresponded rather closely with patients uncomplicated by pregnancy Although these authors hesitate to conclude that pregnancy is devoid of any influence on breast cancer, they do suggest that other contributing factors may be of greater importance

Following a careful review of the world literature White (25) found only 920 cases of breast cancer occurring during pregnancy or lactation An additional 22 cases were currently reported from three large New York hospitals The five year survival rate for this collected series of 734 cases of breast cancer treated during pregnancy or lactation was only 17 1 per cent and the ten year survival rate was 11 4 per cent This survival rate is obviously poor and scarcely comparable to the prognosis for patients with breast cancer uncomplicated by pregnancy White states somewhat conservatively that 'the results in this group of patients are not as good as among the uncomplicated carcinoma of the breast patients ' Also, White noted that the gross survival rate among patients in whom pregnancy followed adequate treatment of breast cancer was about the same as in patients in whom pregnancy did not occur as a late complication of postmastectomy patients. This author concluded "It is probable that pregnancy is not contraindicated in patients with treated carcinoma of the breast without noticeable metastases" There is every reason to believe, however that patients with a more advanced disease either die before becoming pregnant or are urged by their physicians and surgeons to prevent the possibility of pregnancy Thus, these survival statistics noted by White probably represent a highly selective group of patients in whom the natural history of the disease has already taken its toll prior to the onset of pregnancy Similar factors make it difficult to eliminate the unintentional "built-in bias" of almost all statistical studies pertaining to this subject

One of the most revealing studies of this subject is a recent report by Cheek (5) In a survey of current expert opinion concerning breast cancer and pregnancy Cheek submitted a questionnaire to 55 specially selected physicians in the United States and abroad The clinical opinions of these specialists whose interests have been closely identified with the problem of breast cancer are of considerable value They constitute the essence of past experience, for in the coexistence of these conditions no one man is sufficiently experienced by himself The

questions asked and a brief summary of the answers given follow·

1. How many cases of carcinoma of the breast developing during pregnancy have you seen? In how many was a "five year cure" obtained?

A total of only 151 cases were personally observed during pregnancy The five year "cure" rate was exceedingly low, being only 5 3 per cent This response confirms the opinion that breast cancer coexisting with pregnancy is a relatively rare occurrence with a decidedly poor prognosis

2 Should carcinoma of the breast developing during pregnancy be considered inoperable?

None of the responses indicated that pregnancy alone would render the disease hopelessly inoperable Although pregnancy complicating breast cancer cannot be regarded in itself as an absolute criterion of inoperability, yet the five year survival following surgery is certainly disappointing

3 In the premenopausal age, does pregnancy following a previous radical mastectomy increase the chances of development of carcinoma in the remaining breast?

Most investigators indicated that subsequent pregnancy did not favor the development of cancer in the remaining breast

4 Should pregnancy be terminated in a patient in whom carcinoma of the breast develops in the first trimester, in the second trimester, in the third trimester? Would you expect the five year cure rate to be increased by the termination of pregnancy?

It was generally conceded that pregnancy should be terminated as soon as the diagnosis of breast cancer is confirmed Special conditions may merit individual consideration particularly when religious convictions or the tenets of faith are concerned If cancer of the breast is discovered during the third trimester of pregnancy, a viable child may be obtained by the induction of premature labor or by a Porro Caesarian section A representative group believed that the five year survival could be increased by the termination of pregnancy Critics of this point of view contended that the potential of the pregnancy stimulus probably placed the patient in jeopardy before the tumor became clinically evident

5 Should sterilization or tubal ligation be done following radical mastectomy in the premenopausal woman to prevent further pregnancies?

The majority of the responses indicated that neither tubal ligation nor sterilization following radical mastectomy was advisable Conventional contraceptive measures were considered adequate to prevent future pregnancies Most physicians thought that subsequent pregnancies should be avoided because of the possibility of reactivating residual tumor cells The majority were in accord that castration should be reserved as a therapeutic measure for recurrent or metastatic disease

Discussion

Thus, a review of the literature reveals a disconcerting lack of uniformity of opinion regarding the practical aspects of this problem. The number of cases observed by any one investigator is comparatively small, and the clinical material is extremely varied and heterogeneous Most authors are of the opinion that pregnancy should be terminated or lactation discontinued upon the discovery of a coexistent breast cancer, but there is little or no agreement, however, as to the optimum method or time of this interruption The question of subsequent pregnancy following breast cancer has been regarded differently by many clinical investigators However, each has observed only a relatively small number of cases and none has proved to be the prophet of prognosis

Since cancer cells can lie dormant for a number of months or years it seems reasonable to suggest that pregnancy be avoided following breast cancer for at least a period of several years Whereas the literature reveals contradictory opinions concerning the prognosis or the optimum period for postponing pregnancy, there is virtual agreement concerning the value of immediate radical mastectomy *in cases which are considered clinically operable* In 1904 Oster (20) first expressed the opinion that mastectomy was the treatment of choice in cases of early breast cancer discovered during pregnancy However, Haagensen and Stout (12) in 1943 strongly suggested that certain cases of breast cancer should be considered 'categorically inoperable" Their experience had led them to conclude that radical mastectomy in this group of patients (including all women who developed breast cancer during pregnancy or lactation) was futile More recently however Haagensen (11) has modified these original criteria of operability While still regarding the results of surgery in women with breast cancer and pregnancy or lactation as disastrous he now concedes that radical mastectomy may be 'justified in these patients provided, of course, that the disease is locally operable"

Although pregnancy or lactation when combined with breast cancer adds peril to the prognosis, Adair (1) does not regard it as a contraindication for radical mastectomy In the record of his experience at Memorial Hospital (including patients who became pregnant postoperatively) a five year survival following radical mastectomy was noted in 44 per cent of the cases In addition to favoring *radical mastectomy* during pregnancy or lactation when of course, the lesion was considered operable (only 50 per cent were operable) Adair (2) has indicated that if the pregnancy is promptly terminated the five year survival may be considerably improved The importance of therapeutic abortion appeared to be in enhancing the five year survival rate

Summary and Conclusions Regarding Therapeutic Recommendations

It is readily apparent that the discovery and diagnosis of early breast cancer is difficult indeed during pregnancy or lactation because of the tremendous growth stimulus and physiologic engorgement of the breast at this time The dictum of DaCosta declares that breast biopsy is mandatory in any patient with an enlarging mass or with a mastitis of pregnancy or lactation that persists despite treatment This is a particularly sound surgical precept in this era of efficient antibiotic therapy

Radical mastectomy is considered the treatment of choice in all tumors which are regarded as operable regardless of the prospects for ultimate survival Therapeutic abortion promptly following or preceding radical mastectomy is recommended by the author during the first trimester of pregnancy Therapeutic abortion per vagina or abdominal hysterotomy plus radical mastectomy is advised during the second trimester of pregnancy *However the diagnosis of breast cancer must be absolutely ascertained by biopsy in all cases prior to the interruption of pregnancy* Breast biopsy and radical mastectomy may precede the termination of pregnancy depending upon the extent of surgery required for the interruption of pregnancy and the period of convalescence contemplated between operations Abdominal hysterotomy is the operation of choice during the second trimester but therapeutic abortion per vagina may be undertaken until about the twelfth week Removal of the malignant tumor without undue delay is always a prime consideration During the third trimester of pregnancy the

problem presented by each individual patient merits particular attention The ardent parental longing for a viable child should take precedence over all other considerations A Porro Caesarian section or the induction of premature labor has been recommended for this period

The risk of radical mastectomy late in pregnancy may be formidable but not forbidding and can only be determined for each patient by the conjoint clinical judgment of both the surgeon and the obstetrician "In great straits and when hope is small, the boldest counsels are sometimes the safest " Breast cancer discovered during lactation should receive prompt surgical therapy, and the lactation should be suppressed as soon as possible Patients with advanced breast cancer who are considered "categorically inoperable" when first seen should be treated intensively by means of radiotherapy to the breast and regional lymph node areas, regardless of the presence of pregnancy The termination of pregnancy in these patients is a matter of choice to be decided upon in accordance with the desires of the husband and wife

Castration by either surgical or radiologic means should be reserved under ordinary circumstances as a therapeutic and *not* prophylactic measure (to be used for recurrent or metastatic disease) However, in the case of a more advanced and extensive yet clinically operable lesion, there may be sound justification for surgical castration during abdominal hysterotomy Here the indication may appear to be prophylactic but in reality is probably therapeutic, for the couriers of cancer so often extend beyond the clinical ken In the categorically inoperable case where termination of pregnancy is contemplated, surgical castration should be a concomitant procedure

In the absence of any trustworthy guide to prognosis, it does not seem justifiable (except under unusual circumstances) to jeopardize the life of the mother by allowing her to bear additional children The calculated risk and uncertainties of a subsequent pregnancy should be undertaken with a clear understanding of its guarded prognosis It has been the author's practice to advise patients who desire to become pregnant following radical mastectomy to wait at least three years if axillary metastases were not present at the time of operation and five years if axillary metastases were present For in the matter of prognosis "tis better to bear the ills we have than fly to others we know not of "

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CHAPTER XVIII

Self-Examination of the Breast

Introduction

"Fight Cancer with Knowledge"

The art of cancer education consists not alone in our knowing the value of early diagnosis and treatment but also in imparting that knowledge to the public Despite the great zeal for current cancer education, there remains much to be accomplished in dispelling the pall of public ignorance about this dire disease Is the armor of education adequate to arouse curiosity and stimulate interest in the common danger signals of breast cancer? Until the development of a specific and reliable diagnostic test for cancer all of us must grow increasingly alert to malignancy on the slightest clinical evidence For although a small breast tumor which is discovered early is no guarantee of curability, yet the destiny of this disease favors such a probability There is nothing quite so simple as to believe only that which we wish to believe However, the record of our experience with public instruction does indicate a genuine desire and popular willingness to practice the principles of prophylactic self-examination

The Importance of Early Detection and Diagnosis

Cancer incidence rates indicate that breast cancer in the female is undoubtedly the commonest single organ site of predilection (see Chapter XIX) It comprises 20 per cent of all cancer in women However, despite the fact that the breast is a readily accessible surface organ, only two out of five cases of breast cancer are currently discovered while the tumor is still localized to the breast alone It is readily apparent that the current breast cancer "cure" rate lags far behind the theoretically possible "cure" rate if all available knowledge were applied at the earliest possible time The correlation between duration of disease, size of tumor, stage of disease and ultimate prognosis is sufficiently well defined to justify our utmost effort in attaining the earliest possible detection and diagnosis Despite our failures with this method it is the *best* we know at present—an initial and most important step in our ultimate good

In the treatment of breast cancer the concept of *early diagnosis* and *prompt surgical therapy* is a sovereign precept which affords the highest hope of greatest benefit When the primary tumor is small and the disease is limited to the breast alone, a five year clinical "cure" rate approaching 80 or 90 per cent can be anticipated In its earliest stages cancer of the breast seldom produces pain or makes its presence known by any other readily recognized warning symptom Thus, the main method of detection must rely upon the regular examination of the breasts in women who are entirely symptom-free This program of examinations should

FIG 146 Portrait of a young woman practicing self-examination of her breast (used with permission of The Cancer Bulletin)

be made monthly in order to discover new lesions at the earliest and most favorable time The technique of self-examination is easy to learn and can be conveniently fitted into the normal routine of life

Contemporary cancer education programs have resulted in an increasing interest on the part of the public for periodic health examinations. However these physical examinations, valuable as they are performed perhaps annually or even once every six months cannot be the bulwark of defense for the entire population The total number of all adult women who would present themselves often enough for a cancer detection examination (facilities permitting) to assure the earliest possible diagnosis is inconsiderable If breast cancer is to be detected in time it is the responsibility of the woman herself to be the first to find it A woman can often locate breast abnormalities more readily than her doctor can

The enthusiastic advocate and sponsor of the idea of breast self-examination in the United States has been C D Haagensen of New York who graciously credits the late Hugh Auchincloss with initially making this technique a maxim among his patients. In his careful studies of breast cancer Haagensen (5) has noted a mean diameter of 4.8 cm in the clinical tumor size of a consecutive series of 608 primary breast cancer cases admitted for treatment to the Presbyterian Hospital The total incidence of axillary metastases in this series approximated 70 per cent In contrast with this

unselected group, a highly selected series of cases were carefully chosen in which the clinical tumor size measured less than 1 5 cm in diameter The incidence of axillary metastases in this specially selected series was only 11 per cent Therefore, since prognosis and ultimate survival is directly proportional to the incidence of metastases, its correlated relation to tumor size and duration of disease is readily apparent If teaching women the technique of self-examination results in an earlier detection of breast cancer, then constant vigilance is a pittance to pay for the price of health

THE FILM "BREAST SELF-EXAMINATION"

An excellent educational film in color and sound entitled, "Breast Self-Examination" has been produced in recent years by the collaborative efforts of the American Cancer Society and the National Cancer Institute of the Department of Health, Education and Welfare This cancer control motion picture teaches women the importance of examining their own breasts by a simple technique of inspection and palpation The method is patterned after that which physicians usually employ and requires only a few minutes of time *practiced regularly once a month* In sponsoring the routine health habit of breast self-examination, the vital force of public education is carried across a significant threshold—it endeavors to make every *home* a cancer detection center The film has been shown to thousands of women throughout the nation during the past few years Great editorial care was taken in planning this audiovisual cancer control aid to prevent the possibility of exciting cancerophobia

Technique of Breast Self-Examination

The essential features of breast self-examination are those employed routinely by most physicians and consist primarily of a regular monthly health habit of inspection and palpation (see chapter VIII) The technique is short and simple but based upon long experience

Self-examination should be practiced only once a month shortly after the menstrual period when the breast is least engorged and physiologically "at rest" The time of day for this examination is much less important than the regularity of performance However, a sleepless night of anxiety may be avoided if the examination is performed in the morning.

INSPECTION

Careful inspection before a mirror requires but a few minutes of time and teaches women the landmarks and normal appearance of their breasts (fig 147) Reassurance regarding simple inversion of the nipples or the normal asymmetry of both breasts is often required Inspection of the breasts with the arms elevated and with the arms lowered (figs 148 & 149) will accentuate the danger signal of skin or nipple retraction. The significance of nipple discharge or "crusting," eczema excoriation of the nipple should be stressed A change in breast contour will often reveal an underlying breast cancer of moderately small size

PALPATION

Palpation of the breast is first done with the self-examiner lying flat in bed with one arm elevated above her head Gentleness and thoroughness are prime requisites for this most important step in self-examination The entire breast of one side is carefully palpated with the flat of the fingers of the opposite hand The examination should begin at the clavicle and extend to below the breast, first medially and then laterally The same procedure for breast self-examina- is then performed on the opposite side Examination of each breast with the arm

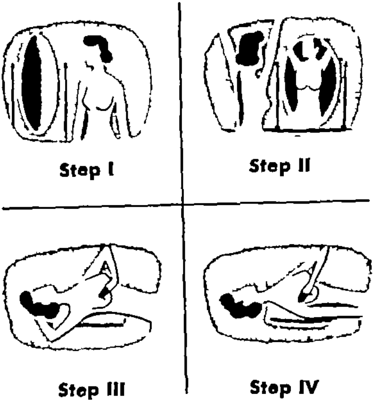


FIG 147 Silhouette of self-examination by steps (used with permission of the American Cancer Society)

lowered at the side of the body is then repeated (fig 150)

During the examination of the upper and outer quadrant of either breast some tenderness or thickening may be discovered in the axillary tail of the breast This is particularly common during the premenstrual period Solitary or discrete nodules are to be stressed as findings of importance rather than pain or tenderness Undue concern in self-examination is occasionally associated with a palpable inframammary ridge or a thickened costochondral junction in a thin woman

As suggested by Haagensen (4) ' It is advisable for women to follow a definite technique such as has been described for self-examination and to adhere to the routine of this technique In this way they will become familiar with the physical characteristics of their breasts as revealed by repeated palpation with this one preferred method and they will also be more likely to identify any small carcinoma that may develop in the breast "

If a lump is felt or an abnormality seen by the patient she is urged to see her doctor at once The patient must be warned that repeated massage may be dangerous and the procrastination of delay may be disastrous

Evaluation of Breast Self Examination

A comprehensive survey has been reported by Lewison Jones, Doran Mandel Harrison and Daniels (6) for the specific purpose of evaluating the effectiveness of the film Breast Self Examination ' in cancer education A large group of women employed by a federal agency were shown the film under standard conditions and similar circumstances Some six months after seeing the film about 2 300 of these women were individually interviewed by means of a specific questionnaire designed to assess the value of self-examination The results of this study are summarized as follows

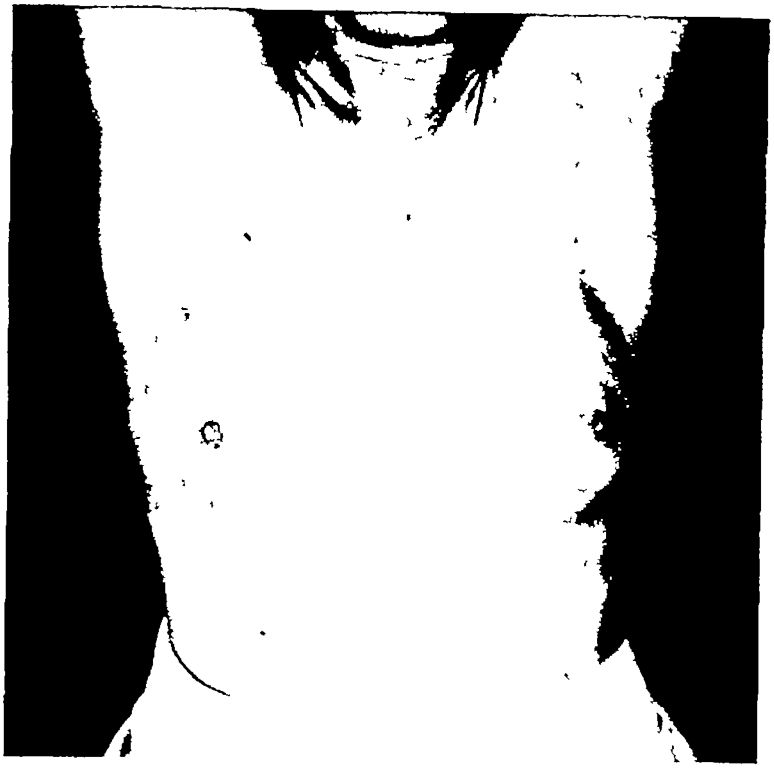


Fig 148

Figs 148 and 149 Self-inspection of breasts with arms elevated and with arms lowered showing normal contour and appearance

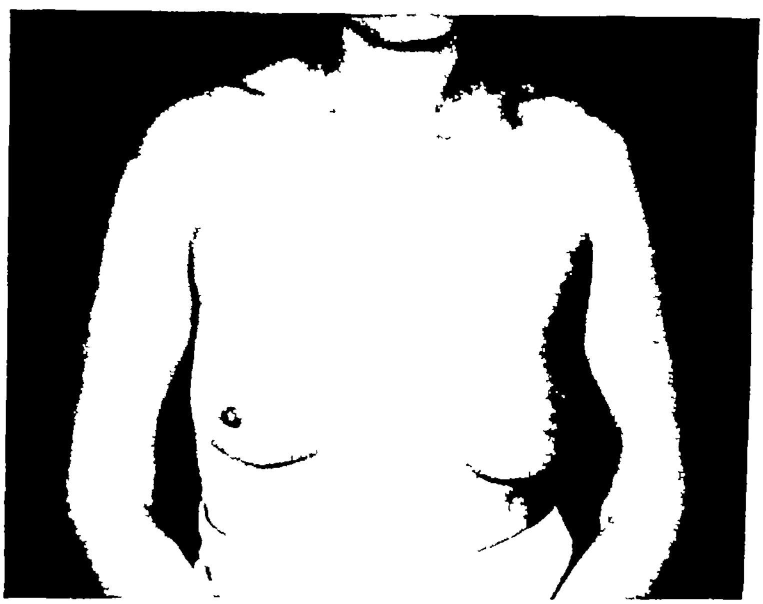
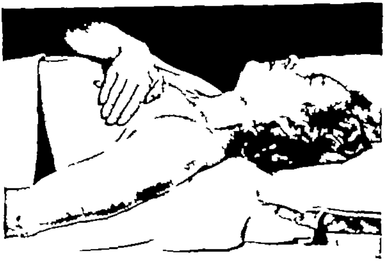


Fig 149

A Prior to seeing the film only 7 8 per cent of this group of women indicated that they had ever examined their breasts, whereas since learning the technique of self-examination more than 80 per cent practiced self-examination with some degree of regularity (table 74) About 25 per cent of the group examined their breasts on a regular monthly basis It was surprising to find that women with a previous history of breast disease, thus presumably making them more breast conscious, were somewhat less receptive to the teaching of self-examination than the group at large Such diverse factors as marital status, parity, race, work grade or academic level produced

FIG 150 Self-examination by palpation with the arm lowered The side being examined is slightly elevated on a pillow



no major significant deviation in educational response

B The technique of self-examination was practiced most frequently during early adult life and least frequently later in life (table 75) At about the age of 55 when the prevalence of breast cancer is just past its peak, there appeared to be an unexpected and unexplained lessening of interest in the health habit of self-examination

C In answer to the direct question, What did you learn from seeing the film Breast Self Examination ' the written replies were classified as shown in table 76 The results of this inquiry indicate a favorable reaction in 93 per cent of the replies and an unfavorable reaction in only 6 4 per cent of the replies The latter represents learning's labor lost.

D Whereas only three per cent of this group of women discovered a definite abnormality within their breasts yet 24 per cent consulted their doctor for a more thorough examination of their breasts. Perhaps the differentiation of a 'lump from a lumpy' breast may at times require a more expert professional examination

E. Cancer education places an enormous responsibility upon the diagnostic skill and cancer detection vigilance of the general practitioner This responsibility is the heritage of the medical profession Prior to seeing the film only 110 women had ever had a breast operation In the six month period since seeing the film there had been 15 women who had already undergone surgery Whereas biopsy and surgical excision of discrete and solitary breast tumors is recommended as the treatment of choice, yet great care and caution must be exercised to prevent excessive or needless surgery

F *Three women reaped the rewards of self examination by discovering their own breast cancers This constitutes a threefold increase in the incidence of breast cancer between the expected incidence for this group of women over this period of time and the actual incidence*

TABLE 74

Summary Data on Rate of Self-examination Before and After Film

Self-examination Habit	Before Film		After Film	
	Number	Per cent	Number	Per cent
Total	2 358	100 0	2 358	100 0
Occasionally or frequently	184	7 8	1 902	80 7
Not at all	2 161	91 6	447	19 0
Not reported	13	0 6	9	0 3

TABLE 75

Effect of Film on Women, by Age Group

Self-examination Habit	Total		Under 25 years		25–34 years		35–44 years		45–54 years		55 years & over		Unknown age	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Before film	2,358	100 0	410	100 0	963	100 0	601	100 0	274	100 0	100	100 0	10	100 0
Occasionally or frequently	184	7 8	17	4 1	67	7 0	58	9 7	28	10 2	13	13 0	1	10 0
Not at all	2,161	91 6	393	95 9	895	93 0	541	90 0	243	88 7	87	87 0	2	20 0
Unreported	13	0 6	0	0 0	1	0 0	2	0 3	3	1 0	0	0 0	7	70 0
After film	2,358	100 0	410	100 0	962	100 0	601	100 0	273	100 0	100	100 0	12	100 0
Occasionally or frequently	1,902	80 7	345	84 1	797	82 8	464	77 2	226	82 8	67	67 0	3	25 0
Not at all	447	19 0	65	15 9	165	17 2	137	22 8	47	17 2	33	33 0	0	0 0
Unreported	9	0 3	0	0 0	0	0 0	0	0 0	0	0 0	0	0 0	9	75 0
Rate of response to film*		80 0		83 5		81 5		74 8		80 5		62 1		—

* Calculated by dividing number without self-examinations before film into the number in this group with self-examinations after film

TABLE 76

	Number	Per Cent
I Nothing, very little	227	5 15
II How to examine breasts, that self-examination is possible or easy	3,407	77 3
III Importance of early detection and regular examination	503	11 43
IV Other answers	270	6 12
A Favorable	188	4 2
B Unfavorable	56	1 3
C Indeterminate	26	0 6

Conclusions

Breast self-examination is an effective means of discovering those small and presumably early cancers which cast their shadows before them Although cancer education is frequently held responsible for creating cancerophobia, yet a provident regard for cancer and its detection may be the mother of early diagnosis and life-saving surgery A salutary idea must not be blamed for the fear or folly of its followers Breast self-examination is by no means a divining rod, but by its routine practice women will find today what would be all too obvious tomorrow

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CHAPTER XIX

The Statistics of Breast Cancer

Magnitude of the Problem

The misery of mankind from malignancy in general, and womankind from breast cancer in particular, is one of society's saddest burdens Among today's captains of the men of death, cancer and the cardiovascular diseases (fig 151) have the sinister distinction of reigning supreme Cancer is exceeded at present only by the cardiovascular diseases as the leading cause of death In 1950 in the United States there were 210,733 deaths from cancers of all sites and 18,973 of these recorded deaths were from breast cancer Using data collected in ten representative urban areas, it has been estimated that the annual number of newly diagnosed cases of cancer in the United States can be currently considered to be about 497,000 Cancer of the female breast constitutes about 54,000 of these newly diagnosed cases In New York state (exclusive of New York city) breast cancer is the most frequently reported malignant tumor In women throughout this country breast cancer is the most frequent single organ site of cancer, and it is the leading cause of death for women between the ages of 40 and 60 years

The epic of past experience has grimly indicated that cancer of the breast has never been at a loss for occasions and it is not unreasonable at present to forecast its continued malevolence This disease has a long and painful past history, a dire present and, unavoidably thus far, also a future

Limitations of Statistical Data

For effective study and control of cancer it is important to bring the facts and figures into sharper focus, yet it is well to be aware of the limitations, fallacies and inadequacies of these statistical data Spurious estimates of cancer increase may be due to improved diagnostic facilities, a wider application of surgical techniques or more accurate death certification In considering the limitations of data based upon mortality statistics, it must be carefully borne in mind that the ordinary medical certification of death is not a clinical history The certifying physician is not expected to report those illnesses (either past or present) which do not directly bear upon or contribute to the cause of death Physicians can hardly be expected to note on a death certificate that the decedent was a "cured" case of breast cancer Medical certification of death is sometimes made by a physician whose contact with the deceased patient has been very limited indeed Although the postoperative appearance of a case of breast cancer is readily apparent, yet the clinical details of the terminal illness might have been entirely unknown Death due to occult breast cancer or remote metastases may be difficult or impossible to diagnose with any degree of accuracy without the opportunity for special study

Despite an ever-increasing flow of valuable information (from such important sources in the United States alone as the

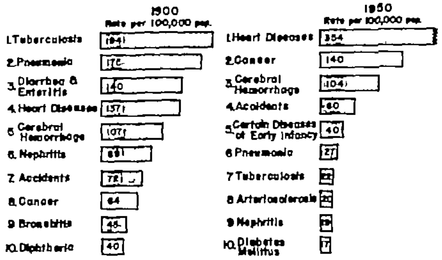

FIG 151 Leading causes of death in the United States 1900 and 1950 In the period 1900 to 1950 cancer has become the second leading cause of death Source National Office of Vital Statistics, Statistical Research Section

National Cancer Institute, National Office of Vital Statistics, U S Bureau of the Census, State Health Departments and the American Cancer Society) concerning the size and nature of the current cancer problem, the validity of these statistical data as they concern cancer and the health of the nation still leaves much to be desired Further refinement in reporting and the increased accuracy of cancer diagnosis and morbidity statistics will undoubtedly come to pass, but there is no reward in waiting for perfection This mathematical millenium may be the inheritance of our posterity

Illustrating the need for caution in interpreting cancer mortality data is the direct ratio shown to exist between the death rate from cancer and the relative number of doctors (fig 152) This close correlation correctly infers that the accuracy and completeness of medical statistics may be dependent upon the number of doctors avail

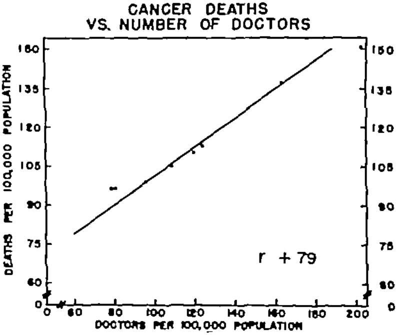

FIG 152 The accuracy and completeness of death certification and vital statistics generally are dependent upon the number of doctors in relationship to the population Each point in the graph shows the cancer death rate standardized for age sex and race and the relative number of doctors for one of the 48 states 1939–1941

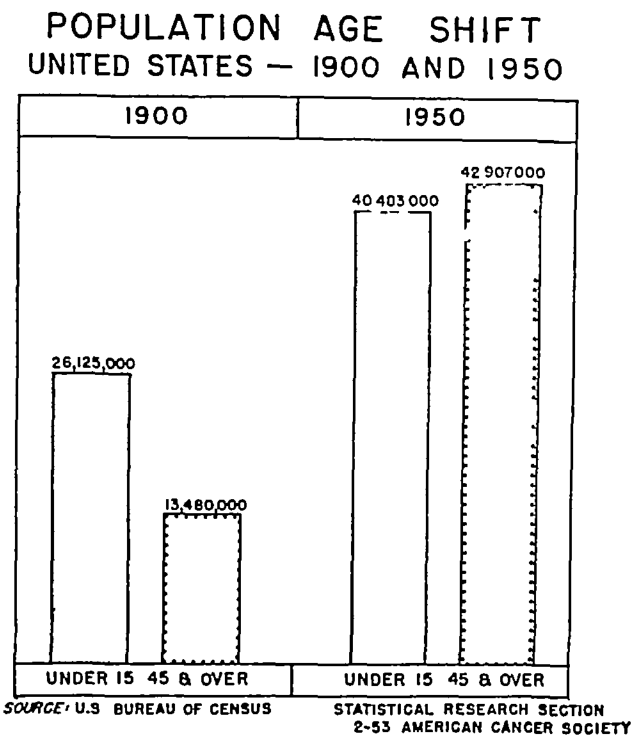

FIG 153 Population age shift in the United States, 1900 and 1950

able for competent diagnosis, treatment and death certification Incorrect and distinctly unfavorable inferences regarding this relationship are, however, possible In the analysis of vital statistics the interpretation of figures which are at the mercy of numerous influences must be critically considered and regarded as cautioned by Hill as "arithmetic guided by logic"

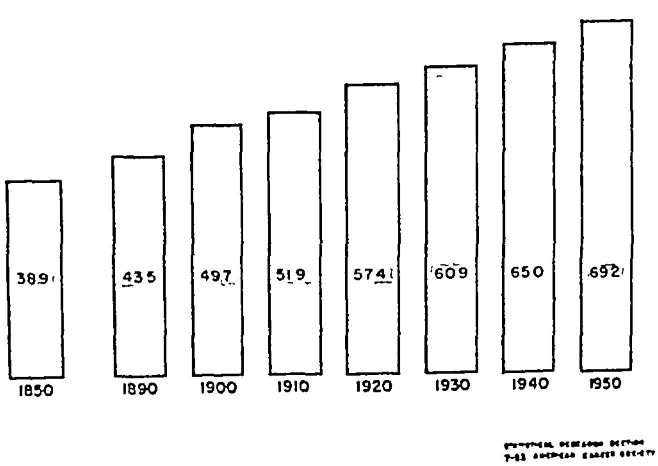

FIG 154 Number of years of life expectancy among the white population of the United States, 1850–1950

Definitions

Statistical comparisons depend upon the following definitions for a clear understanding of cancer data

INCIDENCE

The number of cases first diagnosed (including cases first recorded from death certificates) during a calendar year per 100,000 population

PREVALENCE

The number of cases known to have had cancer at any time during the year per 100,000 population

MORTALITY

The number of deaths during the year for which the primary cause of death was cancer per 100,000 population

It is also necessary to make a clear distinction between percentage distribution of cases of cancer (relative frequency) by age, color, site and sex, and incidence Incidence can only be obtained by relating newly diagnosed cases to a population exposed to risk

Population Trends

During the past 50 years striking changes have occurred in the morbidity of all types of cancer Noteworthy among the prime factors responsible for the over-all increase in cancer incidence and prevalence is the advancing age of the population as a whole (fig 153) This is mainly due to the steady decline in the death toll from infectious diseases (fig 155) among the young and middle-age groups An accurate appraisal of the rapidity of increase in the population trend of the United States alone requires a lively imagination An analysis of these changes, actual and propsective, are graphically presented by Cohn and Lingg (8) in fig 156 The magnitude of this increase is

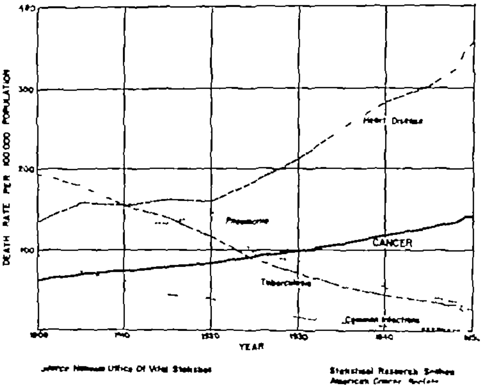

FIG 165 Death rates of selected diseases United States 1900–1950 Since 1900 there has been a steady decline in the death rate from infectious diseases and a steady increase in the death rate from heart disease and cancer

clearly obvious not only in the gross total but in the increasing size of the older age groups as well. Similar evidence of a rapidly aging population is almost universally confirmed by the Vital Statistics Report of the World Health Organization (table 77) With regard to the changes in the size of the population in the United States between 1900 and 1940 Cohn and Lingg point out that the increment of per cent increase is greater at each succeeding generation (table 77a)

The United States Bureau of the Census has currently published in its Population Estimates (9) the projected population of the United States by age and sex from 1955 to 1975 This forecast of the female population above the age of 30 is shown in table 78 Whereas in 1950 there were only 2 133 000 women 75 years of age and over by 1975 it is estimated that there will be 4,571 000 women in these advanced years. The average annual per cent rate of growth of the entire United States population is projected to be between 1 08 per cent and 1.51 per cent for this period

Based upon the cancer morbidity survey of the National Cancer Institute the breast cancer incidence in Philadelphia per 100 000 women between the ages of 45 to 64 was found to be 162 5 Applying this figure to the population projection in table 78 one can calculate that in 1950 there were about 25,000 newly diagnosed breast cancer cases between the ages of 45 and 64 in the United States and in 1975 one can predict that there will be almost 37 000 newly diagnosed cases (ages 45 to 64) of breast cancer annually

Among every 100 000 residents in the Philadelphia area 341 cases of cancer were diagnosed for the first time during 1948 compared to an incidence rate of 271 per 100 000 in 1938 The prevalence rate which

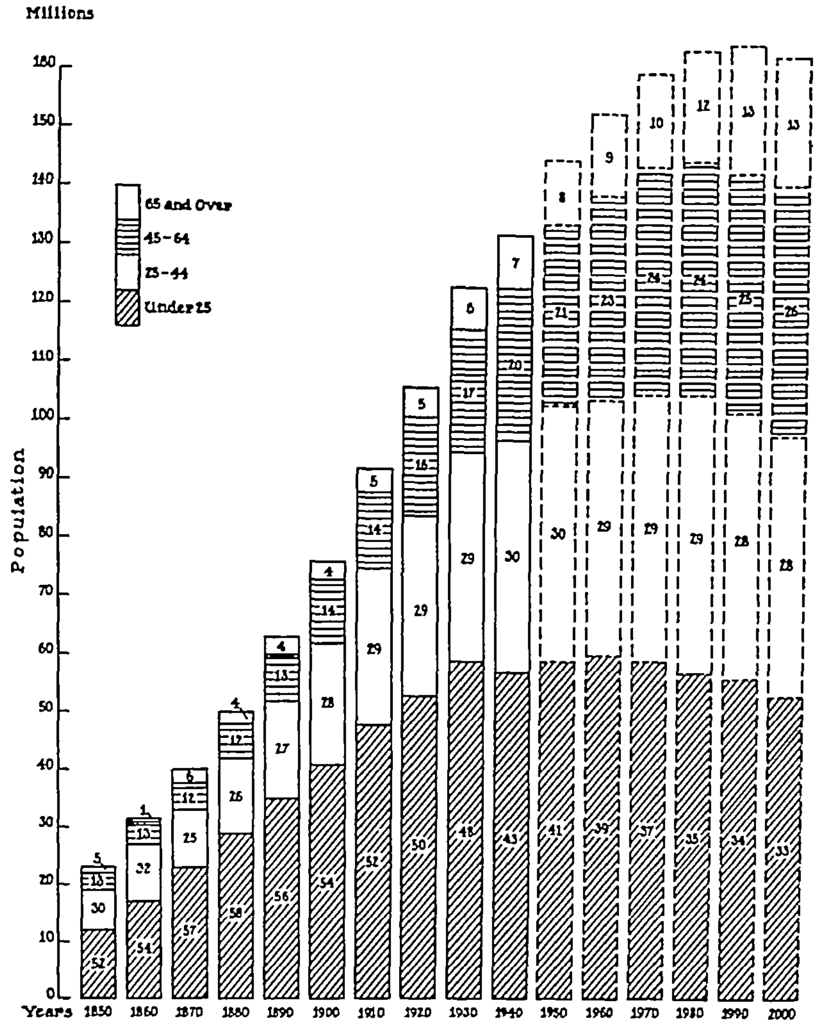

FIG 156 The population trends and changes within various age groups are shown for the United States from 1850 to 1940 The dotted lines show the extrapolation of population percentages to the year 2000

includes all cases with cancer during the study year regardless of the year in which the diagnosis was made, increased from 397 to 482 between 1938 and 1948 and the mortality rate increased from 145 to 165 per 100,000 population Adjustment for the aging of the population between 1938 and 1948 reveals a residual increase in incidence of 13 per cent, an increase in prevalence of nine per cent, and an increase in mortality of only one per cent How much of this residual increase is real and how much is due to such factors as improved diagnosis and reporting is difficult to determine

Breast Cancer Mortality

Regarding mortality in the United States alone the annual number of cancer deaths is now well over 200,000, and if recent trends continue (fig 157) it will increase at the rate of 5,000 annually, or three per cent per year It seems quite likely that the real mortality and the total number of cancer cases are actually much larger than that indicated by collected data derived only from death certificates A small number of deaths are incorrectly diagnosed as cancer and this results in some slight overreporting However, a much larger number of deaths are incorrectly diagnosed due to (a) deliberate omission of cancer from the death certificate, (b) failure to report cancer when it occurs in conjunction with some other major disease, (c) errors in the diagnosis of both manifest and latent cases of cancer, and (d) failure to report "cured" cases of cancer, all of which result in gross

under reporting While the validity of these mortality statistics in their crude state is thereby reduced in value, yet over the course of years the accuracy of vital statistics has shown a steady improvement and is a real measure of educational advance and public health progress.

The prevalent number of actual cancer cases during any standard period of time should be the sum of (a) all deaths from cancer whether diagnosed or not, plus (b) the number of "cured" cases of cancer, plus (c) latent or occult cancer present in patients dying of unrelated causes In evaluating the cancer problem Steiner (47) has estimated the total cancer morbidity in the United States (1948) as noted in table 79 If breast cancer is responsible for nine per cent of all cancer deaths (fig 158) and 18 1 per cent of all female cancer deaths (fig 159), then by subtracting the "estimated cures" the total breast cancer deaths in 1948 can be calculated to be about 23,734 This figure is more probably an under than an over-estimation

The mortality rate (crude) per 100 000 population for breast cancer among females in the cancer morbidity survey for Philadelphia (1948) was reported as 32 1 The death rate recorded by the Vital Statistics of the United States (1950) was 24 6 (table 80) This was appreciably higher than any other single organ site in the female. The corresponding mortality rate for stomach cancer in the male was 25 7 and for lung cancer in the male it was 24 6 Deaths due to cancer of the entire female genital system (uterus cervix and ovaries) combined had a mortality rate of 34 9 which was only moderately higher than for the breast alone

Incidence of Breast Cancer

Accessible and inaccessible organs responsible for the incidence of cancer by sex and

TABLE 77

Proportion of Persons Aged 60 Years and Over for Every 1 000 Inhabitants

About 1900	About 1949	Countries[a]
78	129	Germany
75	159	England and Wales
95	159	Belgium
99	131	Denmark
76	144	Scotland
82	101	Spain
82	108	Finland
124	163	France
107	146[f]	Ireland (Republic of)
96	118	Italy
100	135	Norway
92	114	Netherlands
96	99	Portugal
119	149	Sweden
93	138	Switzerland
34[b]	94[f]	Union of South Africa
77	111	Canada
64	59[e]	Chile
64	116	United States
82[d]	76	Japan
62	125	Australia
68	137	New Zealand

Not including Uruguay for which the last available census was 12 X 1908

[b] Census of 1904

Census of 1907

[d] Census of 1903

Census of 1940

[f] Census of 1946

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TABLE 77a

Population	1900	1940	Per Cent of Increase
Below age 25	41 016 090	56 893 430	39
From 25 to 44	21 297 427	39 672 246	86
From 45 to 64	10 390 976	26 084 276	151
Above age 64	3 080 408	9 019 314	193
All Ages	75 994 575	131 669 275	73

TABLE 78

Projections of the Female Population of the United States, Including Armed Forces Overseas, by Age, July 1, 1955, to 1975, with Figures for July 1, 1950

Age	(In thousands)					
	1950	1955	1960	1965	1970	1975
years						
30–34	5,911	6,308	5,969	5,477	5,680	6,780
35–39	5,743	5,923	6,324	5,971	5,479	5,682
40–44	5,165	5,728	5,914	6,301	5,949	5,459
45–49	4,566	5,117	5,682	5,953	6,236	5,888
50–54	4,159	4,473	5,028	5,571	5,738	6,114
55–59	3,625	4,021	4,341	4,869	5,394	5,556
60–64	3,035	3,426	3,823	4,118	4,619	5,117
65–69	2,590	2,750	3,124	3,478	3,747	4,202
70–74	1,804	2,203	2,362	2,680	2,984	3,215
75 and over	2,133	2,551	3,136	3,574	4,064	4,571

site are shown in fig 160 While the frequency of cancer for all ages combined is about the same for males and females, this is not true throughout the entire life span (fig 163) A similar difference in age distribution can be noted in cancer mortality among the causes of death (fig 164)

The resident breast cancer incidence rate (age-adjusted) per 100,000 population in the Philadephia cancer morbidity survey for 1948 was 69 0 for females and 0 5 for males This represented a two per cent decrease in incidence when compared to a similar survey made ten years earlier

Dorn (13), in his morbidity studies of malignancy, has estimated that the chances at birth of developing cancer are about 17 per cent greater for females than for males Cancer is more frequent among females in the 30 to 60 age range, whereas the ratio is reversed in the later years of life (fig 163) This is best explained by the relatively large

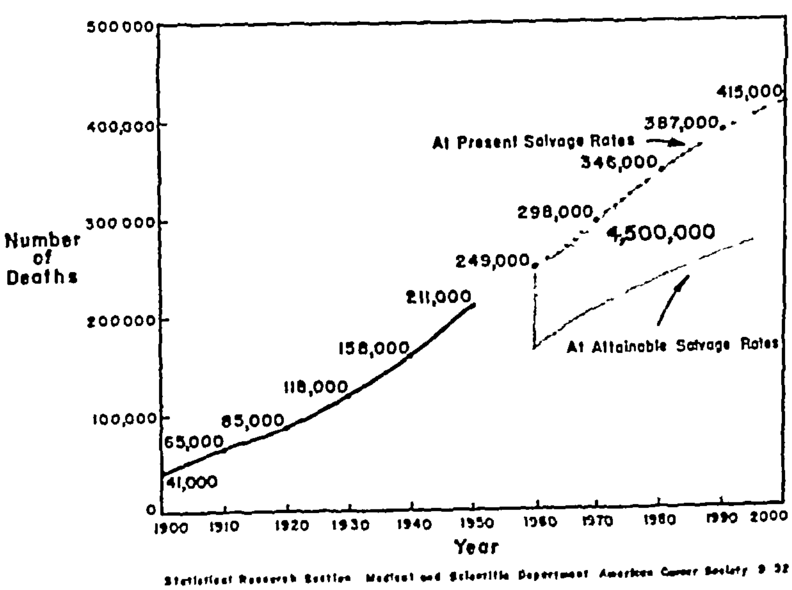


FIG 157 Forecast of cancer deaths and salvage rates (current and attainable) if present death rates continue

number of women with cancer of the breast and genital organs, cancers which develop at a younger age than the predominant forms of male cancers which develop at a later age Nearly 70 per cent of all cancer in females and 50 per cent of all cancer in males occurs in either the breast digestive or genital systems (fig 165) For every 100 women who develop cancer, 46 will have cancer of the breast or genital organs and 23 will have cancer of the digestive system For every 100 men who develop cancer 33 will have a gastro-intestinal malignancy The incidence rates and recent trend for the four leading female cancer sites in New York state is shown in fig 166 According to the incidence statistics of the cancer morbidity survey of ten major cites, breast cancer constitutes 21 7 per cent of all female cancer

Age

Breast cancer appears to be an exuberant and sometimes inextinguishable new growth which arises from the embers of the flagging fires of life Although breast cancer rarely occurs before the age of 20 and is rarely seen after the age of 90, its range of distribution is widespread and its incidence progressively increases with age The percentage distribution by age of the resident cases of breast cancer diagnosed in Philadelphia in 1948 is shown in table 81 At the Vanderbilt University Hospital, Byrd (4) reported that 11 per cent of patients with breast cancer occurred in women over 70 years of age The prognosis following surgery was surprisingly satisfactory River Silverstein and Tope (40) found in a study of breast disease among patients past 55 years of age that 75 per cent of this older clinic group presenting signs or symptoms of breast disease had breast cancer Breast cancer occurs infrequently among males

TABLE 79

Reported cancer deaths	207 721
Estimated unreported cancer deaths	41 500
Estimated cures	23 000
Estimated latent cancers (exclusive of occult prostatic carcinomas)	14 500
Total	286 721

and the major interest in age-specific incidence rates is among females The age-specific incidence rates (cancer morbidity series), shown in table 82 for breast cancer apply to white females *This undeniable proof that the risk of developing and ultimately dying of breast cancer increases continuously with age (figs 162 and 163) is a frequently unrecognized but all important and valid statistical fact*

Results of age distribution will of course, vary depending upon whether hospital records incidence prevalence or mortality rates are used in the computation The hospital age distribution of breast cancer can be expected to be lower than the age distribution based upon mortality rates Shimkin and his colleagues (43) have reported the curious observation that the mean age at initial operation of 261 cases of recurrent breast cancer was 49 5 ± 0 67 years This was significantly lower than the mean age at initial operation of 1,056 cases

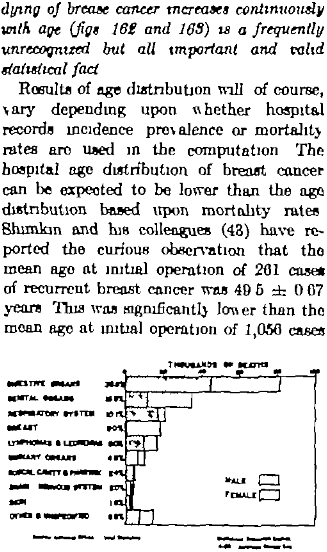


FIG 156 The number of deaths caused by cancer of various sites in both the male and female

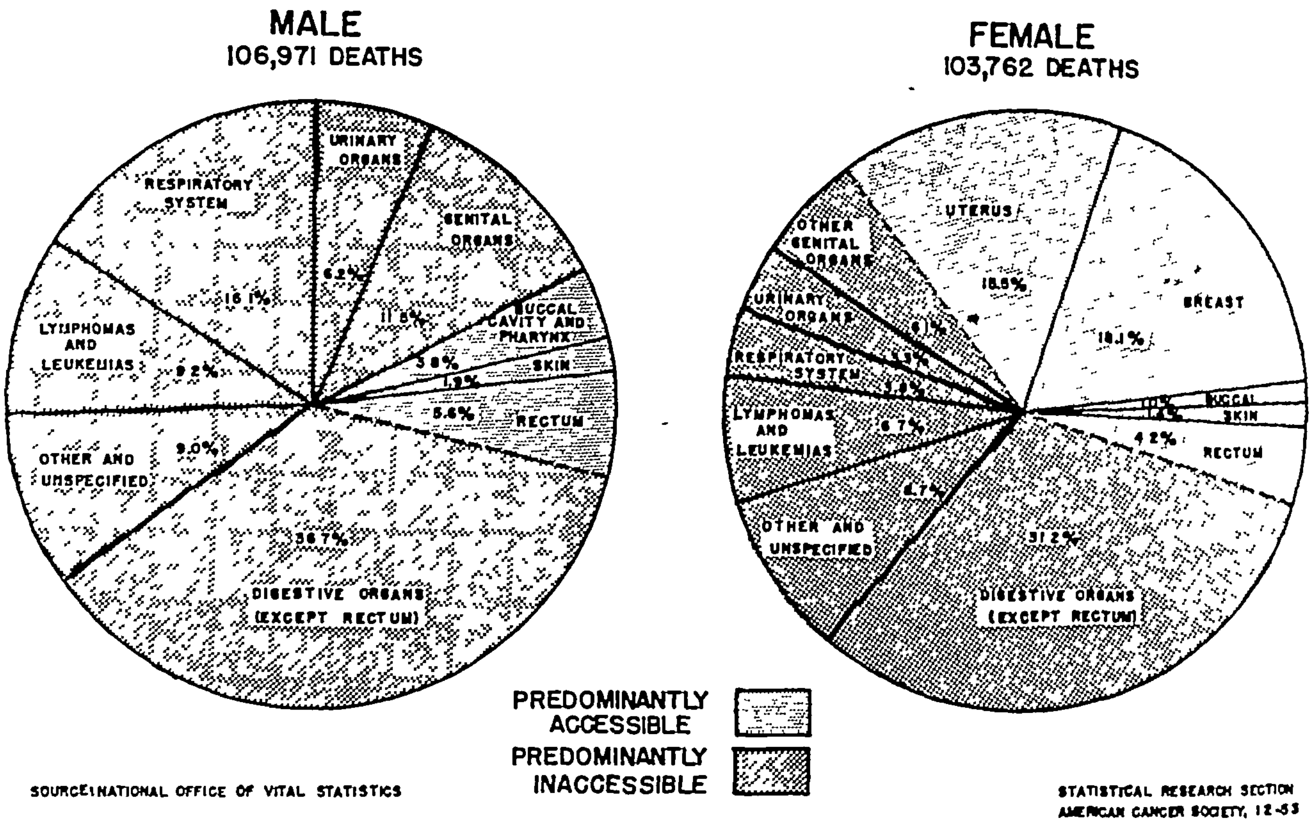


FIG 159 Cancer deaths by sex and site, United States, 1950 In the female, breast cancer causes 18 1 per cent of all cancer deaths It is considered a predominantly accessible organ with regard to the early diagnosis and treatment of cancer

of primary breast cancer (53 9 ± 0 36 years) The largest number of deaths from breast cancer occurs between 55 and 65 Considering the age at operation of the cases treated at the Johns Hopkins Hospital, the greatest frequency of hospital data for breast cancer occurs between the ages of 45 to 55 The average age at operation in our experience was 51 9 years in one series (29) and 53 8 years in a second series (27) Almost 75 per cent of all cases of breast cancer occur in women past 40 years of age In accord with the incidence of cancer of all sites, there is a steadily rising number of new cases annually per 100,000 population from the lowest to the highest age group (fig 167)

All nations in general appear to have similar age-frequency characteristics evidenced by an early period of slowly increasing numbers rising rapidly to a numerical maximum between the ages of 45 to 55 Although the average age at operation in our experience was about 53 years for breast cancer, the average age at operation for benign breast disease at the Johns Hopkins Hospital (28) was 30 years for fibroadenoma, 42 years for chronic cystic mastitis and 47 years for papilloma

Menopausal Period

A singular feature of the age distribution of breast cancer in the Danish Cancer Registry, reported by Clemmesen (7), is the slight decrease in incidence noted in the climacteric period This interesting phenomenon was *not* observed in the rate of incidence of cancer of the cervix or of the body of the uterus Although this variation or "hook" may be merely coincidental,

its relationship to breast tumor regression following the 'hormone imbalance" of castration or sex steroid administration deserves further investigation

As noted by Anderson Reed, Huseby and Oliver (1) accurate information about the age of onset of breast cancer may be significant for both diagnosis and treatment It is possible that such information may aid in establishing important time relationships in the etiology of breast cancer This may be particularly true with regard to the menopausal period and its associated hormone changes Most statistical studies bearing on the age of onset of breast cancer show a unimodal peak in the age distribution curve in the age range of 45 to 50

Some recent data however confirm the bimodal distribution curve of the Danish Cancer Registry reported by Clemmesen Jacobsen (21) studied 200 cases of breast cancer and found two peak periods for the age of onset at 45 to 49 and at 60 to 64 years The records of the Connecticut Cancer Registry reported by Anderson et al also showed a bimodal curve if examined by means of the five year age interval The data from Denmark and Connecticut are particularly significant because they represent relatively complete surveys of large

TABLE 90

Cancer Deaths and Death Rate by Age Sex and Site United States 1950
Malignant Neoplasms of Breast (International List Number 170)

Age	Both Sexes			Male			Female		
	Number of deaths	Per cent of all cancer deaths	Rate per 100,000 population	Number of deaths	Per cent of all cancer deaths	Rate per 100,000 population	Number of deaths	Per cent of all cancer deaths	Rate per 100,000 population
All ages	18 973	9 0	12 5	239	0 2	0 3	18 734	18 1	24 6
Under 5	0	0	0	0	0 0	0	0	0 0	0
5-9	0	0	0	0	0 0	0	0	0 0	0
10-14	1	0 2	0	0	0 0	0	1	0 4	0
15-19	3	0 4	0	0	0	0	3	0 8	0 1
20-24	16	1 5	0 1	0	0	0	16	3 2	0 3
25-29	95	5 1	0 8	2	0 2	0	93	9 7	1 5
30-34	368	12 7	3 2	1	0 1	0	367	21 0	6 2
35-39	825	16 0	7 3	3	0 2	0 1	822	24 0	14 2
40-44	1 451	17 5	14 1	13	0 4	0 3	1 438	27 1	27 6
45-49	1 878	15 1	20 6	17	0 3	0 4	1 861	25 6	40 8
50-54	2 233	12 4	26 9	20	0 2	0 5	2 213	23 1	53 2
55-59	2 372	9 9	32 6	18	0 1	0 5	2 354	20 2	64 9
60-64	2 348	8 3	38 6	38	0 2	1 2	2 310	17 9	76 1
65-69	2 170	7 2	43 2	41	0 2	1 7	2 129	15 7	82 2
70-74	2 007	7 1	53 2	36	0 2	2 2	1 971	15 3	109 3
75-79	1 560	6 8	72 8	20	0 2	2 0	1 540	14 5	134 5
80-84	957	6 4	82 6	21	0 3	4 0	936	13 2	146 0
85 and over	673	8 0	114 3	6	0 2	3 3	665	15 0	191 6
Age unknown	16	—	—	1	—	—	15	—	—

In the specified age-sex group
Source Vital Statistics of the United States 1950 Volume III
Statistical Research Section Medical and Scientific Department American Cancer Society

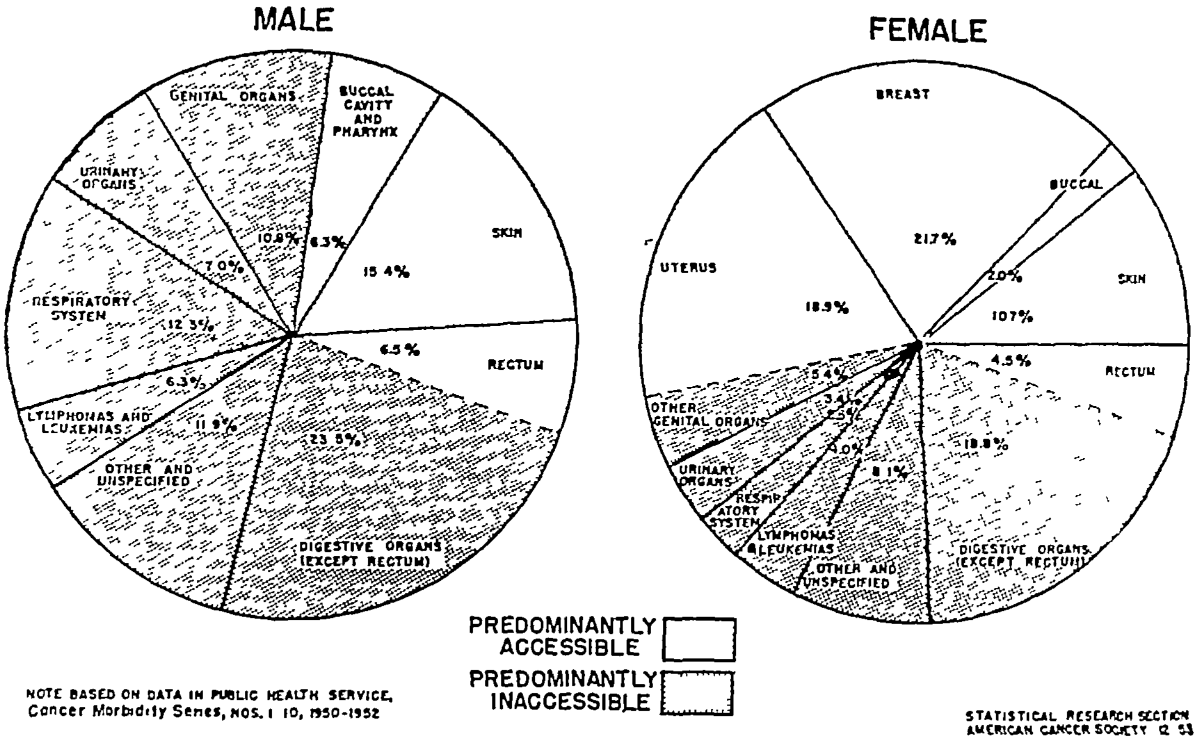


FIG 160 Cancer incidence by sex and site in ten major U S cities, 1947 and 1948

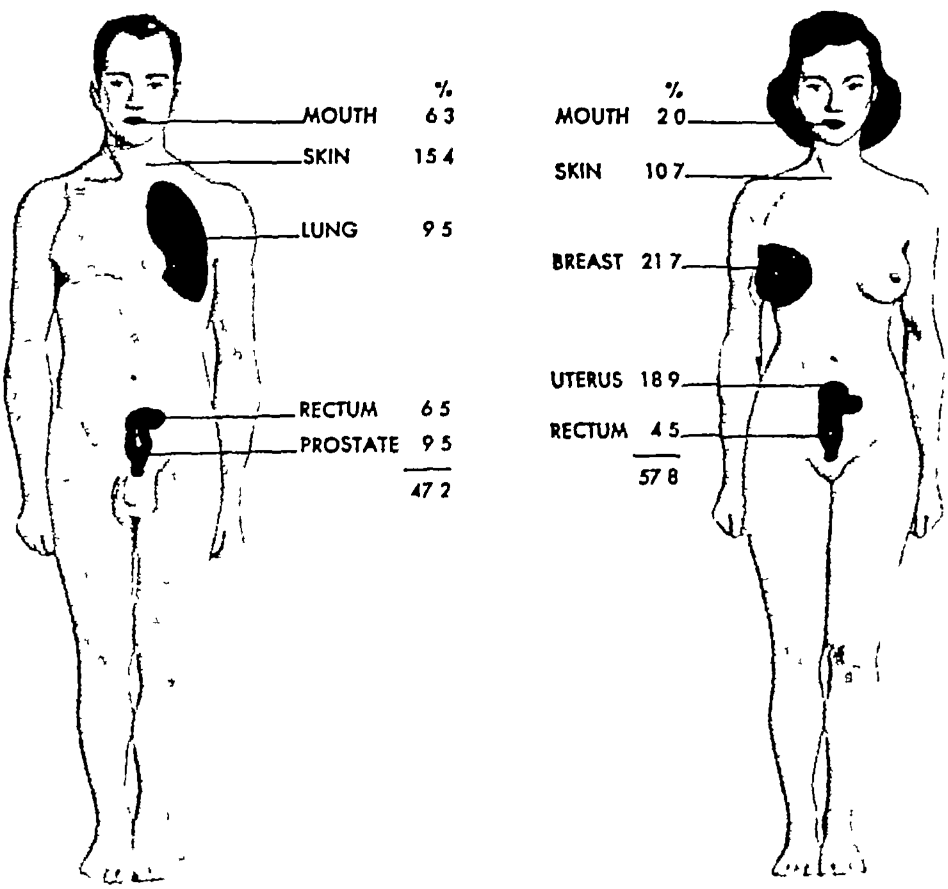


FIG. 161 Cancer incidence of selected sites in the male and the female This data is based upon the survey of ten major cities of the United States by the Public Health Service "Cancer Morbidity Series "

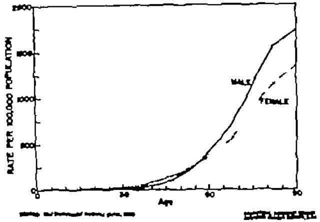


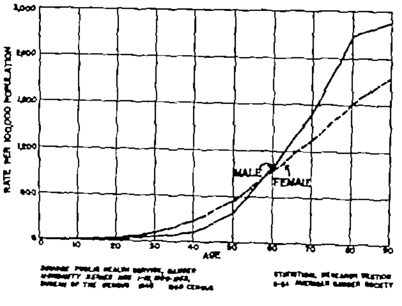
FIG 162 Cancer death rates by age among white males and females United States 1950

populations from widely separated geographic regions. The age at onset of 10 117 cases of breast cancer from Denmark, England and the United States has been graphically shown in fig 163

These studies showing a bimodal distribution of age of onset of breast cancer might indicate the hormonal influence of the menopause on the clinical development and behavior of breast cancer One might speculate regarding this bimodal curve and the unpredictable response to hormone therapy in advanced breast cancer Certain elderly patients with widespread disease may show a striking response to estrogen therapy while younger patients may show a favorable response to androgen therapy Perhaps the two peaks of age distribution represent two distinct types of hormonally dependent breast cancer Careful investigation is required to precisely determine this relationship A complete study of age at onset and age or age-period at menopause for each patient is most important Such accurate data in a suitable series is not readily obtained

Since the breast is often considered physiologically as a satellite of the female reproductive system it would be expected, quite naturally to respond differently to hormonal stimulation during various age periods and differing phases of endocrine activity Many authors have called attention to the importance of the inverse ratio which exists between the frequency of breast cancer and the normal activity of ovarian function Olch (33) computed that 71 7 per cent of normal women pass through their menopause between the ages of 40 and 50 In a study of breast cancer cases he found that almost 55 per cent of the women reached their menopause somewhat later after the age of 50 The average menopause age in Danish women, reported by Clausager Madsen and Ytting varied between

FIG 163 Cancer incidence rates by age and sex ten major U S cities 1947 and 1948



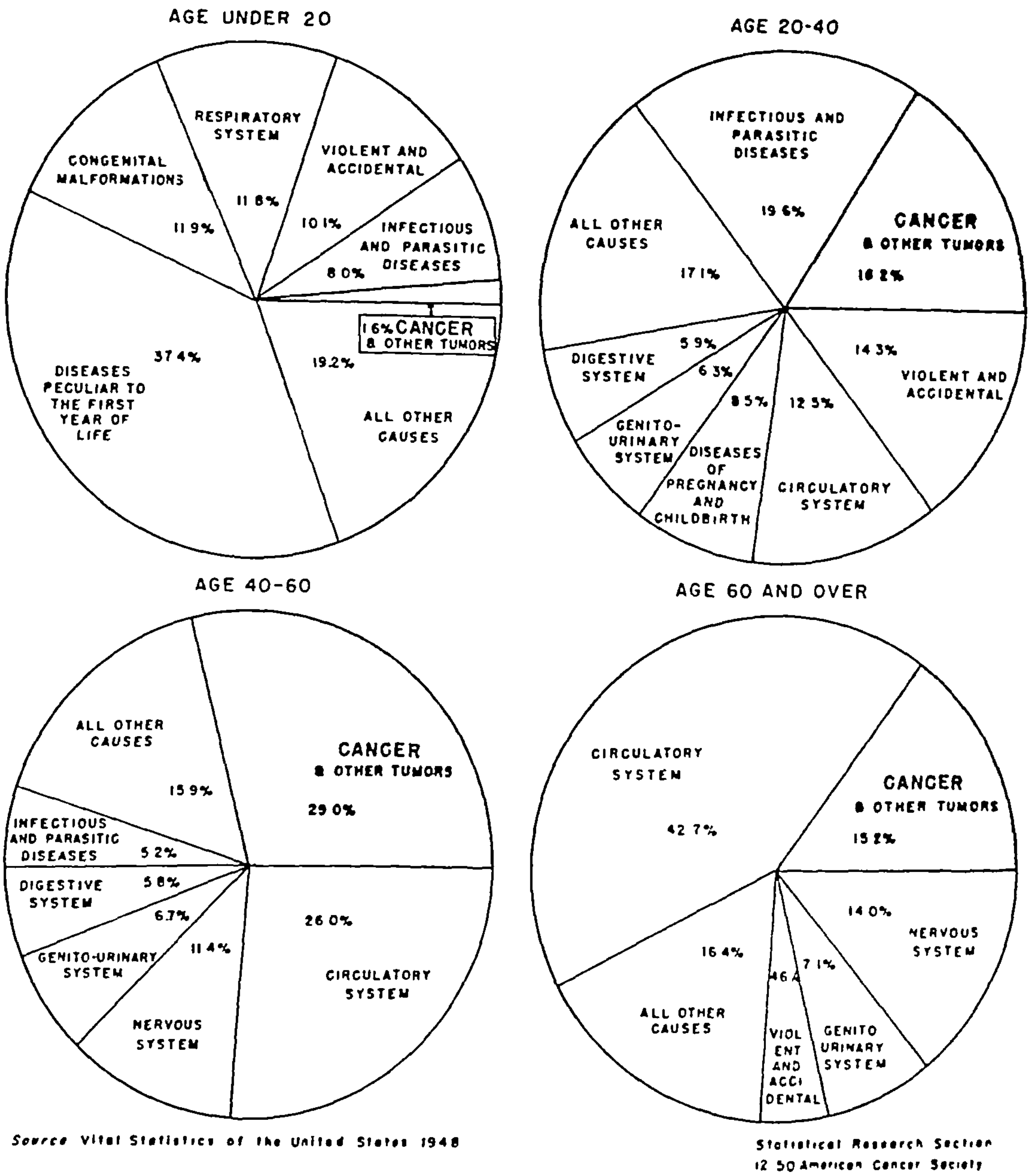


FIG 164 Causes of death among females, United States, 1948 Cancer is the leading cause of death among females between the age of 40 to 60

47 8 years and 48 1 years In Denmark the decrease in breast cancer incidence occurred between 48 and 52 years of age

Race

Cancer morbidity statistics in the United States (5) indicate a slightly lower incidence of breast cancer among non-white females as compared to white females·

	White females	Non white females
Incidence rate	72 6	53 9
Mortality rate	28 2	23 1

It is probable, however, as noted by Dorn, that this merely represents a statistical reflection of less adequate medical care upon which to some extent this cancer morbidity survey was based. Part of the observed difference may be due to differences in the age distribution of the white and non-white population Lower incidence rates for the non-white female may reflect a tendency to delay in seeking medical care A certain proportion of non-white females with breast cancer probably receive no

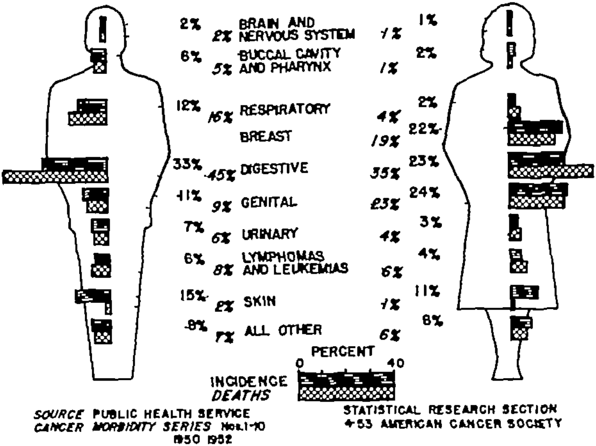


FIG 165 Cancer incidence and deaths by sex and site in ten major U S cities, 1947–1948 More than two-thirds of all cancers occurring in women (and one half of all cancers occurring in men) arise in the breast digestive or genito-urinary organs

medical care whatsoever It would appear unlikely that non white women present basic biologic differences with respect to breast cancer and therefore actually are less susceptible to mammary malignancy

Geographic Distribution

Cancer of the breast appears to have a widespread distribution with no special predilection for climate race or geographical area. Breast cancer is an arrant "world citizen whose cellular turmoil can be found in every part of the United States (fig 169) and throughout the many nations of the world as well (fig 171)

The formidable difficulties in obtaining accurate statistical data and the international variations in reported cancer morbidity are due to many diverse factors. The proof of this is strikingly demonstrated by the selected international summary of cancer death rates shown in fig 172 The complexity of the data and its lack of uniformity on a worldwide basis are accentuated Yet while recognizing the inherent source of error in these international statistics it is of importance to view the disease in its universal perspective for cancer is a ubiquitous scourge which makes a mockery of national frontiers

Although epidemiological studies of infectious diseases have been of immense help in preventive medicine, it is all too clear that there is relatively little accurate information available on the incidence of cancer among primitive peoples The difficulties encountered in the demography of

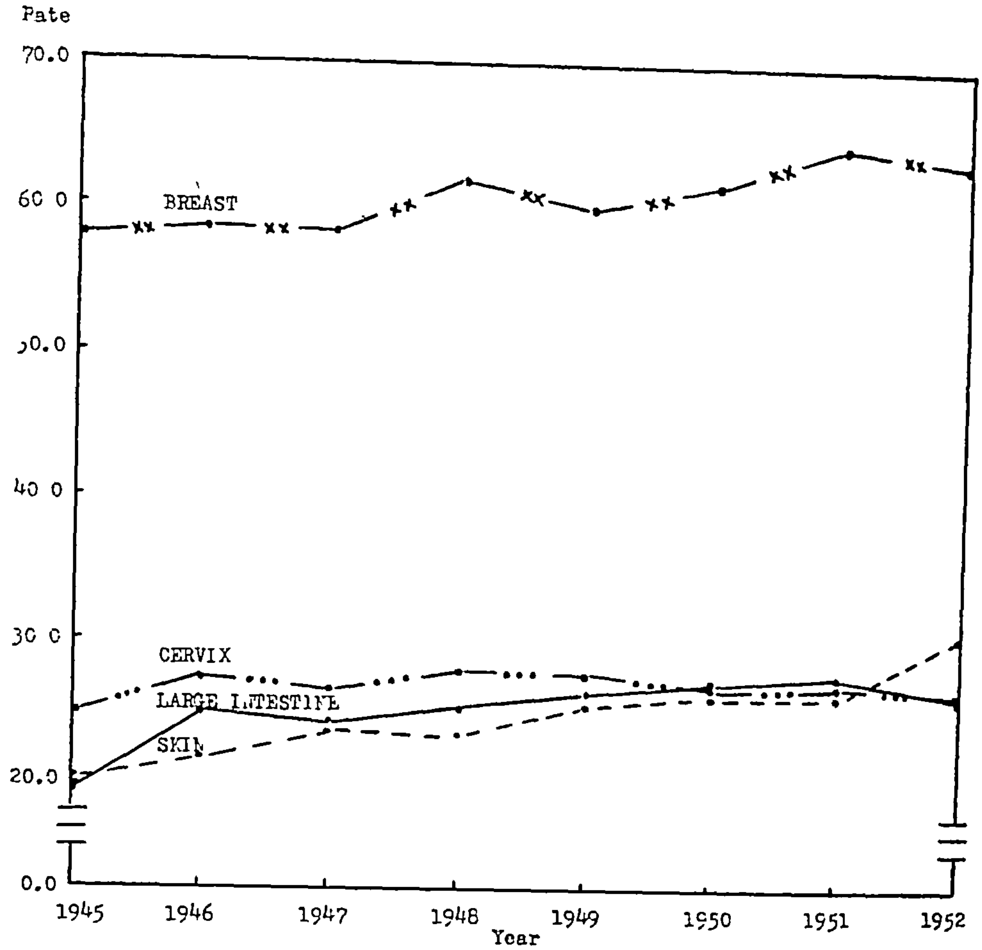


FIG 166 Incidence rates (crude rates per 100,000 female population) for the four leading female cancer sites of 1952 New York state exclusive of New York city, 1945–1952

cancer among Western peoples are magnified many times in more primitive communities

The statistical hazards and handicaps peculiar to rural South Africa have been vividly described by Higginson (19) The relative number of patients in the cancer age group admitted to such native community hospitals is small, while those of a younger age suffering from malnutrition and infectious diseases is large The hospital physician, thus, will see only a relatively few cancer cases in a large number of admissions, and will obtain a false impression of its absolute incidence Histological confirmation of all diagnoses is infrequent but fundamentally essential in all cases of cancer if accurate data is to be obtained In a South African hospital caring for a predominantly urban Bantu population, it was found that only 17 per cent of the total number of admissions were over 45 years of age, the so-called "cancer age" In most large urban hospitals in the United States these middle age and older age groups constitute well over 50 per cent of the patient population

Among the South African Bantus, breast cancer ranks second to cancer of the cervix and fundus of the uterus as the most common cancer of the female Higginson states that "it is probable that the proportion would be greater if there were more females in the older age groups in the series examined "

Khanolkar (22) noted that in India breast cancer was "far more common in women belonging to communities with late mar-

riages in women and a relatively better economic position The cancer incidence in Indonesia reported by Kouwenaar (24) indicated that the over-all frequency of cancer was about the same as in the United States and Europe, provided that the age distribution of the population was taken into account In Java cancer of the breast and uterus were reported as the most common tumors in the female Tumors occurring in Thai and Chinese patients observed in Bangkok Thailand have been reported from the departments of pathology of two Bangkok medical schools by Vellios Goonchorn and Suranatemiya (49) The malignant tumors of the breast including cystosarcoma phyllodes constituted the largest group of the series (12.8 per cent) There were 53 tumors in women and one in a man The peak age incidence occurred at 50 years. Seventeen specimens of fibroadenomas were also seen Breast cancer was the most common malignant tumor observed However increasing scientific interest in cancer's epidemiology indicates a low incidence of breast cancer among Japanese women Steiner (53) noted an incidence among Mexican women which was less than in Caucasoids

Statistical data reported by Kook (23) from Israel indicates a high rate of occurrence of breast cancer among Jewish women as compared to Israeli women of oriental extraction The presumed increase among Ashkenazic Jewish women is ascribed to late marriage and birth control A high incidence of cancer occurred in the family history Caucasian race countries of Europe and the Americas report little difference or variation in breast cancer morbidity

Geographic pathology is a new and promising field for the investigation of human cancer Special intensive studies in selected fields, as noted by Symeonidis (48) which show a significant variation in clinical cancer

TABLE 81

No of Cases	Per cent								
	All ages	Under 15	15–24	25–34	35–44	45–54	55–64	65–74	75 and over
827	100 0	0	0 6	4 2	14 6	23 0	24 1	20 9	12 6

may lead to the direct or indirect recognition of etiological factors The importance of differences in customs nutrition, endemic diseases and endocrine patterns should be studied in relation to cancer A recent conference on Geographic Pathology and Demography of Cancer was held at Oxford, England for the purpose of studying the geographic variations in the incidence and behavior of cancer It was evident from the reports of this conference that the age-corrected morbidity of breast cancer among different ethnic groups and geographic regions varied only within the inherent limits of each investigation Breast cancer is an ancient and elusive disease of global distribution which continues to claim its many victims from every country in which cancer morbidity is recorded throughout the world

Laterality of Breast Cancer

The evidence of Clemmesen (7) Busk and Clemmesen (3) and Lane-Claypon (25) in a large series of cases indicates that breast cancer is more frequent on the left than on

TABLE 82

Age	Incidence Rate	Age	Incidence Rate
0–4	0 0	45–49	139 1
5–9	0 0	50–54	163 1
10–14	0 0	55–59	182 0
15–19	0 7	60–64	225 0
20–24	2 5	65–69	242 7
25–29	9 1	70–74	266 4
30–34	28 9	75–79	354 9
35–39	50 1	80–84	362 0
40–44	97 0	85 plus	367 7

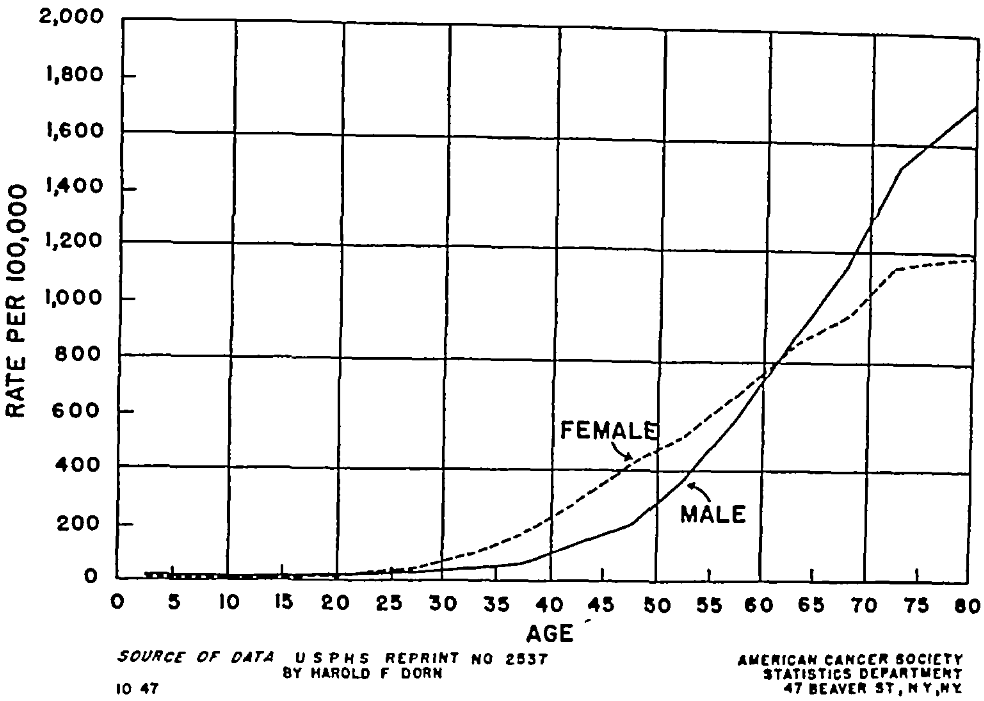


Fig 167 Number of new cancer cases by age and sex per 100,000 white population per year, United States There is a steadily rising incidence of new cancer cases with increasing age

the right in the ratio of about 11 to ten The data of Shimkin, Lucia, Stone and Bell (44), at the University of California, reveal 544 leftsided breast cancers and 509 rightsided lesions This ratio is almost identical with the data found in Denmark, England and Switzerland Although this preponderance is slight, some authors suggest a causal con-

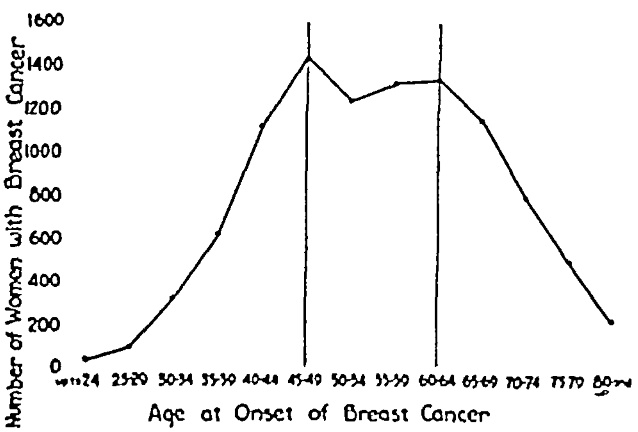


Fig 168 The age at onset of 10,117 cases of breast cancer from Denmark, England and the United States (After Anderson, Reed, Huseby and Oliver (1))

nection with injury which also appears to be more frequent in the left breast It has been demonstrated by Busk that the sisters and mothers of women with breast cancer will tend to develop an eventual cancer at the same site as the patient These observations have been confirmed by Penrose, MacKenzie and Karn (35) It is curious to note that a reversed ratio was found to exist in the author's limited experience with regard to the laterality of benign breast disease A preponderance of patients had benign breast disease on the right

Aberrant Breast Tissue

Schaeffer, in Morris' Human Anatomy (41), reports that aberrant breast tissue occurs in from one to seven per cent of the normal population and is more frequent on the left than on the right This coincides with the frequency of breast cancer on each side A most comprehensive collective review of congenital anomalies of the breast can be found in Deaver and McFarland's

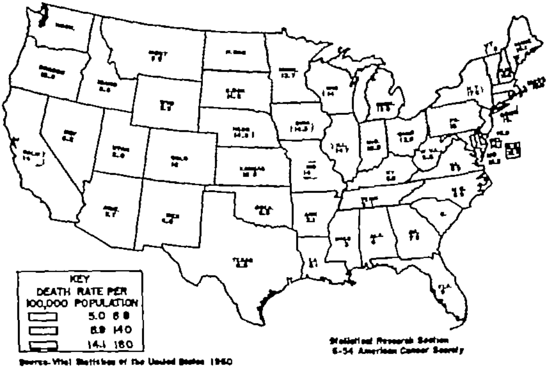
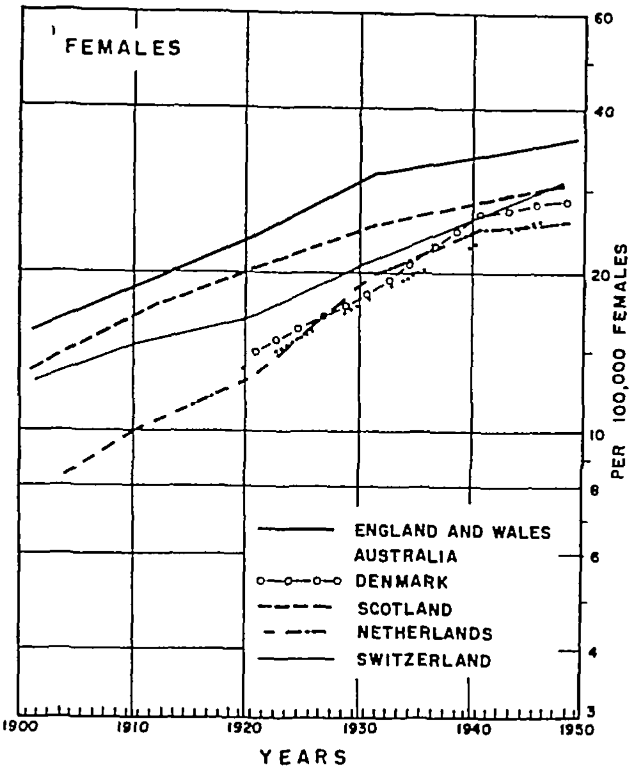


FIG 169 Cancer of the breast Crude death rates 1950

excellent book on "The Breast" (11) where the subject of polymastia, supernumerary or aberrant breast tissue is completely discussed The most frequent location of aberrant tissue is adjacent to the upper and outer quadrant of the breast although it may occur anywhere along the "milk line" from the axilla to the groin Deaver and McFarland have arranged their collected cases by anatomical site and found most of the supernumerary breasts to occur in the axilla, but thoracic or abdominal sites in the "milk line" were not uncommon

Aberrant breast tissue may give rise to breast cancer which is often mistaken for malignancy arising in the upper and outer quadrant of the breast Aberrant tissue does not usually drain into the normal breast as the two are independently formed from separate anlages of ectoderm The high incidence of aberrant thyroid cancer has led Deaton and Bradshaw (10) to speculate

FIG 170 Cancer—all sites Crude death rates 1950.



Epidemiological and Vital Statistics Report
World Health Organization
1952

FIG 171 The international trend of breast cancer mortality appears to be uniform The rise in the early part of this century seems to be leveling off

about the frequency of breast cancer arising in the upper and outer quadrant and its relation to aberrant breast tissue Deaver and McFarland state that there are no data to show how great this danger is

Bilateral Breast Cancer

Bilateral breast cancer occurring simultaneously is infrequent In the author's experience at the Johns Hopkins Hospital, 1 5 per cent of cases were bilateral when first examined Lewis and Rienhoff (26), reviewing an earlier series of breast cancer, found that four per cent became bilateral and 1 5 per cent were bilateral on admission Harrington (16) reviewed 6,559 cases treated by mastectomy in which 62 (0 9 per cent) had bilateral breast cancer occurring simultaneously and 212 (3 2 per cent) developed a breast cancer on the opposite side at some time subsequently Although most patients who develop bilateral disease do so within the first five years, a much longer interval may ensue Finney, Merkel and Miller (14) found six cases (2 per cent) in their series of 298 who had bilateral simultaneous breast cancer Desaive (12), in a study of 1,259 cases of breast cancer, found 55 cases (4 4 per cent) which were simultaneous bilateral breast cancer and 46 cases (3 5 per cent) which were non-simultaneous tumors The incidence of bilateral breast cancer in inflammatory malignancy has been reported as high as 13 per cent Although these frequencies appear generally comparable within limits, nevertheless the criteria of true bilateral cancer varies in each series and the exact time of follow-up (a factor of considerable importance) is seldom uniform

Bilateral breast cancer may be due to two independent and primary tumors arising perhaps as a result of multicentric origin, or bilateral breast cancer may be due to the early or late dissemination of an original malignant tumor The proof of difference between these is often difficult to verify

In a careful consideration of 501 cases of breast cancer, Reese (38) found 20 (four per cent) which were bilateral The clinical and microscopic features of these cases were described and in at least 15 they were believed to be distinct primary tumors Reese concluded that bilateral breast cancers are more often due to two primary tumors than to metastatic dissemination of a single primary growth

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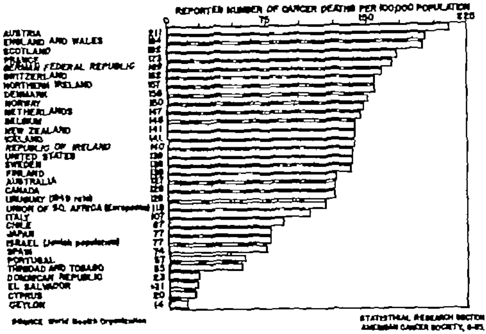


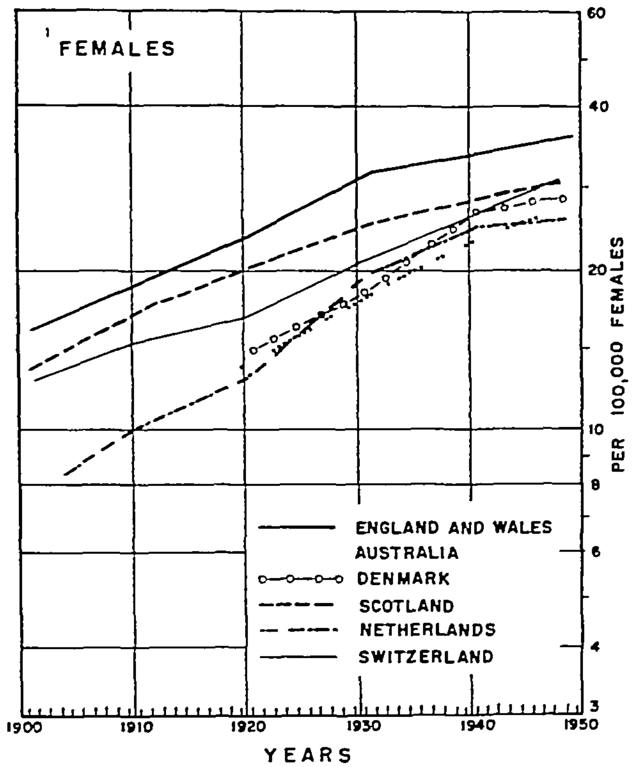
FIG 172 Cancer death rates for selected countries 1950

separate tumor as originally suggested by Billroth The three criteria of individuality of breast cancer, as recommended by Desaive (12) are difficult to ascertain and contingent upon several uncertain premises Any single breast cancer can vary considerably in any one of several microscopic fields and on the other hand two separate breast cancers each from a different person, may be indistinguishable under the microscope

It has been anatomically demonstrated that the lymphatics of the skin of the two areas of the breast are continuous across the midline Clinical evidence of this can be observed in the satellite skin metastases which occur and occasionally extend across the midline (see fig 58 page 179) Metastatic breast cancer involving the opposite axilla or supraclavicular region without apparent involvement of the intervening breast is not infrequently seen Thus, the possibilities of a tumor in the opposite breast representing a metastatic lesion appears quite likely

In a complete and thorough study of multiple cancers arising in patients with primary breast and other cancers, Mider Schilling Donovan and Rendall (32) found their greatest difficulty in evaluating or classifying bilateral primary breast cancer The histological differentiation in their opinion was of comparatively minor importance The predominant breast cancer was infiltrating duct carcinoma which varied considerably in pattern and appearance throughout the tumor More than one half of those patients with bilateral breast cancer were excluded primarily because of site (inner quadrant tumors which were considered more likely to be followed by presumably metastatic breast cancer in the opposite breast) Cancers arising in the medial half of the breast were considered likely to metastasize to the opposite side The great majority of patients in their series, who had primary bilateral breast cancer (beyond a reasonable doubt) had both tumors located in the upper and outer quadrants of each breast

The results of their study (table 83) reveal that a patient who is treated successfully for a specific type of cancer has about the same probability as the non-cancer bearing person of similar age and sex of developing a second primary cancer The presence of cancer in



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The prerequisite criteria for establishing a diagnosis of multiple primary cancer have been discussed by Warren and Gates (51), Slaughter (45), Hubbard (20) and Phillips and Shirey (36) It seems unrealistic to require that each of the bilateral breast cancers be of different histological structure or that distinct metastases occur from each

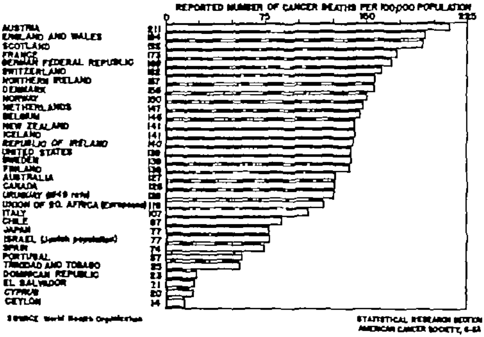

Fig 172 Cancer death rates for selected countries 1950

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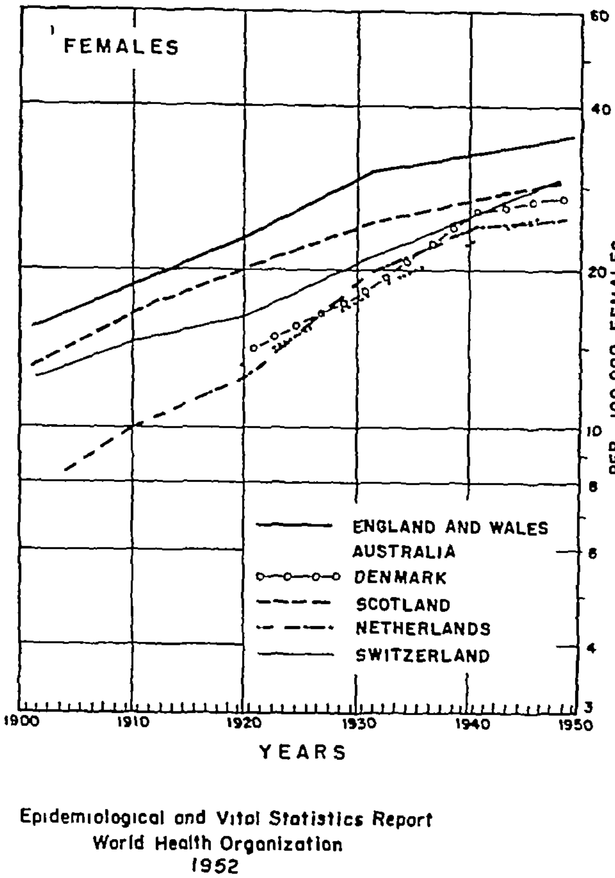

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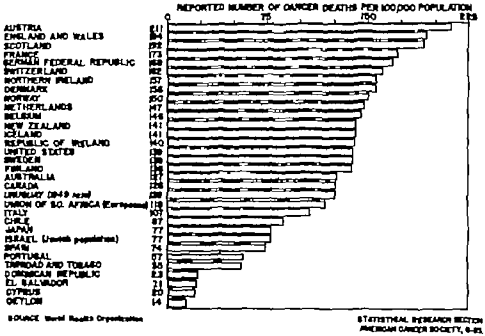

FIG 172 Cancer death rates for selected countries 1950

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TABLE 83

Other Cancers Synchronous with or Following Cancer of a Common Site

Common Site	Experience in Person-Years	Expected No. Cancers			Observed No. Cancers		
		Total	Site		Total	Site	
			Same	Other		Same	Other
Hematopoietic system	1,328	6.8	0.01	6.8	10	—	10
Corpus uteri	1,825	14.2	0.8	13.4	17	0	17
Cervix uteri	2,479	14.2	1.4	12.8	9	—	9
Stomach	1,028	8.9	0.8	8.1	11	1	10
Breast	4,645	32.3	7.2	25.1	53	25	28
Large intestine	3,922	33.5	5.3	28.2	80	40	40

After Mider, Schilling, Donovan and Rendall (32)

one organ does not confer any degree of immunity or prevent the development of cancer in another organ. However, "a second cancer of the same histogenesis may be expected to occur much more often than one would expect on the basis of chance alone."

The predicted incidence of breast cancer in the population studies by Mider et al. was found to be seven individuals of the age and sex surveyed who would be expected to develop primary breast cancer during the period of follow-up. Actually there were 25 second primary cancers (about four times the expected number) which developed in the remaining breast. Patients who died early from their first breast cancer (prior to developing bilateral disease) might have been considered even better candidates to develop a second primary tumor based upon the growth potential of these more serious types. These 25 cases met all of the requisites for primary bilateral breast cancer, but at least 11 other patients with bilateral breast cancer could have been included "on reasonable though possibly more tenuous grounds." It was concluded, therefore, by these authors that *patients with one breast cancer have a significantly increased probability of developing a second primary cancer in the opposite breast.* The risk of developing multiple cancers in different organs in patients with breast cancer is neither increased nor decreased by the presence of a primary mammary malignancy.

In a long-term follow-up study of 116 patients with bilateral nonsimultaneous breast cancer, Harrington (18) reported that 35.1 per cent of the traced patients (114) survived 15 years after their first radical mastectomy and 24.1 per cent survived 20 years or longer following their first operation. These results are paradoxically more satisfactory than those obtained by the same investigator in unilateral breast cancer (see table 34, Chapter X). Harrington finds it "difficult if not impossible, on the basis of present knowledge, to explain the satisfactory results obtained following bilateral nonsimultaneous carcinoma." Host resistance in these patients must be a particularly important factor in their long-term survival despite bilateral disease, perhaps not adequate to prevent onset but sufficient to resist growth or delay the mitotic interval. At least it is of genuine importance and indeed gratifying to know that a second primary breast cancer occurring in the remaining breast is not necessarily a hopeless disease. Patients given the benefit of surgical therapy for nonsimultaneous bilateral breast

cancer (when operable) may obtain a very satisfactory postoperative survival.

Slaughter (45), in a study of multiple cancer, states that "... cancer does not arise as an isolated cellular phenomenon but rather as an anaplastic tendency involving many cells at once ... It suggests that the etiological factor whatever it may be, acts upon all the tissues of one type and may produce anaplastic lesions ..." For some years now a number of serious surgeons and clinical investigators have discussed the problem of whether the incidence of second carcinoma in the remaining breast justifies its routine prophylactic removal at the time of initial radical mastectomy. The incidence of bilateral disease is particularly high in inflammatory breast cancer. Many years ago Bloodgood (2) proposed this practice and more recently, Pack (34) and Hubbard (20) have advocated bilateral amputation in selected cases.

Hubbard has reported the results of simple mastectomy of the asymptomatic remaining breast in a small series of 16 patients with unilateral breast cancer. Minute carcinomas were found in the remaining breast in two cases. However, Hubbard warns that this series is much too small to permit any significant conclusions from this exceptionally high frequency. A larger group of 204 patients followed for at least ten years revealed an incidence of nonsimultaneous bilateral cancer of only 3.4 per cent.

As a practical measure of prevention Hubbard found the inferences strong enough to recommend prophylactic simple mastectomy of the opposite breast for those patients with operable breast cancer who "(a) have a family history of breast cancer or (b) are premenopausal and desire to become pregnant." I do not personally recommend prophylactic bilateral mastectomy (see Chapter XI) but rather favor that all patients should be carefully watched with frequent follow-up examinations.

Bilateral Breast Carcinoma and Breast Sarcoma

Whereas there are numerous references in the medical literature to the coincidental occurrence of carcinoma and sarcoma in the same breast, the independent appearance of carcinoma in one breast and sarcoma in the other is comparatively uncommon. Schwarz (42) reported a patient with carcinoma of one breast who developed sarcoma in the opposite breast three years later. Weiss (52) records a patient with carcinoma of the right breast and sarcoma of the left breast after an interval of 11 years. The patient was alive without recurrence three years following her second radical mastectomy. Wakeley (50) has reported a case of breast carcinoma followed by sarcoma in the opposite breast after an interval of 18 years. Cancer and tuberculosis developing simultaneously within the same breast is a relatively rare occurrence.

Present Trends in Breast Cancer Incidence and Mortality

Current estimates indicate that each year in the average American community of 5,000 residents there will be 12 new cases of cancer (including two women with breast cancer); seven cases will die of cancer (including one woman with breast cancer) and two or three cases of cancer will be 'cured.'

Considering the mortality rate for cancer prevailing at the turn of the century, about one out of every 20 newborn children would be expected to die of cancer. By 1940, about one out of every eight newborn children were expected to die of cancer. Current increase in longevity, both present and predicted, make the prospects for death due to cancer decidedly more ominous. The probability that a newborn child will develop cancer

TABLE 84

Probability of Developing Cancer From Age X on For Selected Female Sites

Based on Cancer Morbidity Reports, New York State, exclusive of New York City 1942–1944

Age x to x + n	Probability of Developing Cancer from Age X on				
	All cancer	Breast	Cervix uteri	Fundus uteri	Ovary
Under 5	227	050	022	014	009
5–9	239	052	023	014	010
10–14	239	053	023	014	010
15–19	239	053	023	015	010
20–24	240	053	023	015	010
25–29	240	053	023	015	010
30–34	241	054	023	015	010
35–39	240	054	023	015	009
40–44	238	053	022	015	009
45–49	233	051	020	015	009
50–54	225	049	018	014	008
55–59	215	046	015	013	007
60–64	201	042	013	011	006
65–69	185	037	011	010	005
70–74	167	032	009	008	003
75–79	149	028	007	006	002
80–84	131	025	005	005	001
85–89	115	024	003	004	001
90–94	107	024	002	003	001
95–99	104	023	002	002	001
100–104	102	023	001	001	001

From Gerhardt, P R, and Goldberg, I D (15) 1951

some time during its life is now estimated to be one out of three or four Although the risk of dying of breast cancer increases steadily with age, the chance that a woman of 35 will eventually die of this disease is about four in a hundred, whereas, the probability of developing breast cancer from the age of 35 on for females is between five and six per hundred (table 84)

Current cancer mortality rates for females indicate that death due to cancer of the breast remains the most common single organ site (fig 173) for malignancy Cancer of the breast in females has shown a progressive increase in the early part of the past half-century as a registered cause of death in almost all nations (fig 171)

Despite the fact that the breast is a readily accessible surface organ (fig 174), only one or two out of five cases of breast cancer are discovered while the tumor is still localized to the breast alone In the 1952 annual report of the Bureau of Cancer Control of the New York State Department of Health, the per cent of new cancer cases reported in an early stage of the disease increased from 27 6 per cent in 1947 to 34 2 per cent in 1952 Cancer of the breast constituted 22 4 per cent of all female death certified as malignant in New York state Based upon new case reports from New York, where stage of disease was indicated, there were only 28 per cent of breast cancer cases first seen in an early stage of the disease in 1952

The trend of breast cancer incidence (age-adjusted rates) in New York State, as reported by Gerhardt and Goldberg (15) appears to be rising and the mortality (age-adjusted rates) appears to be falling While the observed rise in the incidence rates may be due, at least in part, to better reporting or other artificial factors, it is quite likely that there is a real but slight increase in breast cancer morbidity If this increase is factual, then the continued decrease in mortality, as observed recently, would represent an increase in survival Almost 2,000 years ago Celsus said that "only the beginnings of a cancer permit of a cure " Today the correlation between duration of disease, size of tumor, stage of disease and ultimate prognosis following therapy is reasonably well defined, thus justifying our utmost effort in attaining the earliest possible diagnosis (see Chapter XIV) This problem of early diagnosis is as important as it is immense but may prove to be highly rewarding in terms of lives saved

Steiner (47) has suggested that the theoretically possible "cure' rate for cancer could be considerably enhanced by adherence to certain highly desirable (if attainable) Utopian standards Steiner "presupposes that all feasible knowledge of cancer case detection could be put to use that all persons would comply with recommendations on frequent screening regardless of convenience and other considerations that all individuals with first symptoms would promptly go to a doctor, that this physician or consultant would quickly and competently carry out the best known diagnostic and therapeutic measures and that the economic where-with all for these steps would be available to every person"

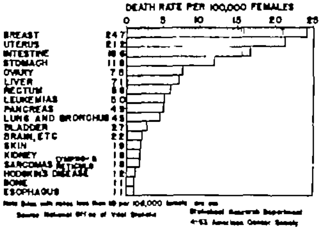

Fig 173 Female cancer death rates by site United States 1950 Cancer mortality rates indicate that among females breast cancer remains the most common cause of death

Noteworthy progress has been made in the field of cancer education cancer facilities and services. A survey of cancer facilities in the United States (6) reveals that in 1950 there were 268 cancer detection clinics, 165 diagnostic clinics and 631 cancer clinics (fig 175) There are at least 17 hospitals in the United States devoted exclusively to the care of cancer patients The film Breast Self Examination,' produced by the National Cancer Institute and the American Cancer Society has proved itself (see Chapter XVIII) to be a relatively effective means of public education Cancer control is now an accepted function of national and local health agencies and is implemented by the many services of the American Cancer Society There are 38 states and territories which have a cancer registry Thirty states and several territories include cancer tissue diagnostic services in their cancer control programs State programs for exfoliative cytology are growing rapidly Cancer clinics approved by the American College of Surgeons and the state programs in cancer

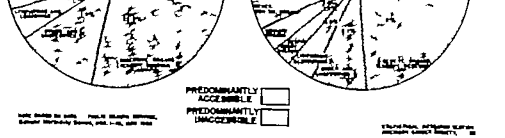

Fig 174 Cancer incidence by sex and site in ten major U S cities 1947 and 1948

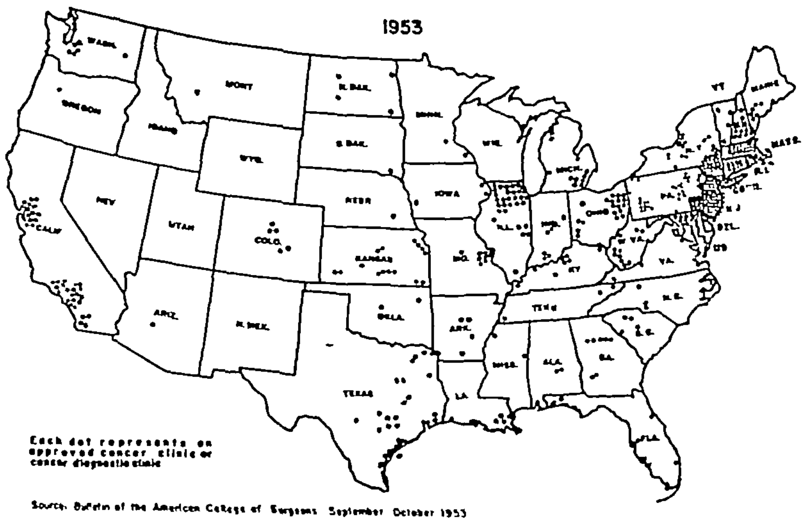

FIG 175 Cancer clinics approved by the American College of Surgeons, 1953

patient follow-up services Expansion of intensive educational programs for the lay public and more active teaching programs concerning the early diagnosis and treatment of cancer in medical schools are all evidences of progress

TABLE 85

Breast Cancer in Females Estimated Annual Death-Rates per Million in England and Wales

Year	Age (Years)					
	0–34	35–	45–	55–	65–	75 and over
1911–20	6	176	474	696	946	1,503
1921–30	7	187	508	782	1,052	1,740
1931–35	8	189	529	839	1,098	1,849
1936–39	8	184	516	830	1,132	1,889
1940–44	9	201	533	823	1,114	1,612
1945	9	198	500	784	1,067	1,590
1946	9	211	531	834	1,122	1,629
1947	9	224	520	785	1,092	1,718
1948	9	211	514	804	1,082	1,712
1949	10	206	493	763	1,112	1,754

"In this table the rates for 1936–39 are derived from the dual tabulation for those years, and those of earlier periods have been adjusted by the appropriate conversion ratios obtained from that tabulation, making each series of rates comparable with those of 1940–44 and 1945" and later

After McKinnon (31) 1952

TABLE 86

Deaths from Cancer of the Female Breast and Age—Adjusted Rates Per 100,000 Population Connecticut 1930–1952

Year of Death	Number of Deaths	Age—Adjusted Rates per 100,000
1930	189	36 1
1931	199	37 1
1932	231	42 7
1933	237	41 1
1934	270	49 6
1935	241	41 6
1936	243	42 2
1937	252	41 0
1938	264	42 4
1939	259	40 8
1940	280	43 7
1941	299	44 4
1942	307	45 4
1943	264	37 0
1944	305	41 5
1945	288	38 8
1946	290	39 2
1947	323	44 2
1948	342	45 3
1949	301	36 1
1950	309	36 2
1951	304	35 1
1952	312	38 3

After Griswold, Dept of Health, State of Connecticut

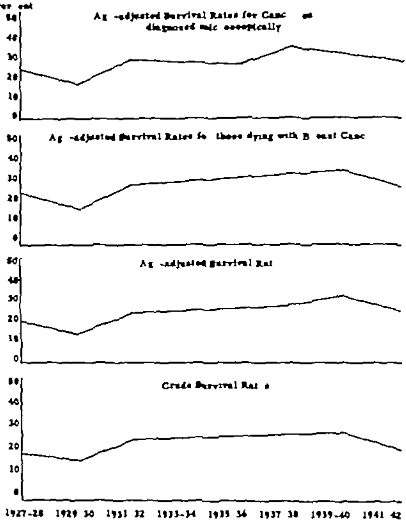

FIG 176 Comparison of ten year survival trends for breast cancer cases compiled by the Division of Cancer and Other Chronic Diseases Massachusetts Department of Public Health 1952 The trends appear to have improved slightly over the period of study (After Lombard Bennett Drake and Quinn (30))

Smithers (40) has recently called attention to the problem of analyzing data based upon death certification but has noted that 'with all these difficulties however if correction is made for the growth of the population and its increasingly adverse age composition a slight downward trend in mortality rate for England and Wales appears.' In commenting upon this slight downward trend in the age-standardized mortality rate of breast cancer Smithers is justifiably cautious regarding its relative importance McKinnon (31) on the contrary favors the explanation that this represents a trend only in the older age groups who are subject to more serious error in death certification In the Registrar General s Statistical Reviews (39) (table 85) McKinnon finds that there has been no significant decline in breast cancer mortality in England and Wales It should also be noted that there appears to be no evidence of an altered incidence of this disease in statistical studies derived from the cancer morbidity survey in the United States.

The importance of early diagnosis and its affect upon the trend in cancer survival has been noted by Pollack (37) In a report showing the gross survival picture among Connecticut residents in whom a diagnosis of cancer was made (1935 to 1948), Pollack found that the five year survival for Stage I cancer of all sites increased from 31 per cent in 1935 to 43 per cent in 1944 No significant improvement over the years was noted for patients with more advanced cancer The over all mortality from cancer of the female

TABLE 87

Corrected Survival Rates Five Years After Clinic Admission—Breast Cancer

(Rate per 100)

Year	Under 50	50–59	60–69	70+	Age—Adjusted to Mass, 1940
1927	14 6	26 1	22 3	27 9	18 0
1928	36 6	32 7	40 7	9 3	34 5
1929	39 2	42 1	32 0	27 4	38 0
1930	24 3	32 7	24 3	22 2	25 3
1931	31 3	34 8	14 4	27 2	29 8
1932	45 2	31 2	50 7	38 1	43 3
1933	50 7	28 8	23 9	21 0	42 8
1934	33 9	20 6	34 6	46 8	33 0
1935	33 7	47 4	43 1	41 8	37 2
1936	40 7	29 1	24 6	41 2	37 5
1937	38 6	24 9	36 5	46 5	37 0
1938	36 0	37 6	39 6	36 5	36 6
1939	42 0	36 3	35 5	29 3	39 6
1940	53 2	30 1	39 7	36 2	47 4
1941	42 2	26 6	28 4	26 3	37 5
1942	35 5	39 4	38 3	39 2	36 6
1943	38 4	39 0	43 9	40 9	39 2
1944	26 2	23 0	42 1	31 5	27 8
1945	42 1	24 1	39 0	49 3	39 8
1946	35 5	45 3	48 6	44 7	39 1
Trend coefficient	0 42	0 06	0 78	0 95	0 45
σ Trend	0 33	0 30	0 33	0 32	0 25
Trend/σ trend	1 3	0 2	2 4	3 0	1 8

After Lombard, Bennett, Drake and Quinn (30) 1952

breast for Connecticut from 1930 through 1952 (table 86) shows some annual fluctuation but no striking trend in either an upward or downward direction

The report of Lombard, Bennett, Drake and Quinn (30) indicates an improvement in the breast cancer situation as shown by a study of the 4,248 female cases of breast cancer observed at the Massachusetts cancer clinics from 1927 to 1950 inclusive. The percentage of cases unconfirmed by microscopic examination has decreased both in toto and in the four age groups studied The percentage of survivals appears to have increased slightly over the period (fig 176) The greatest improvement has been noted in the over 70 years of age group (tables 87 and 88) These investigators suggest that a "part of the improvement among the aged is due to an increase in radical operations, and among the young, the effect of the extensive educational program "

The medical statistics of the Metropolitan Life Insurance Company indicate an encouraging 11 per cent decline in mortality

TABLE 88

Corrected Survival Rates Ten Years After Clinic Admission—Breast Cancer

(Rate per 100)

Year	Under 50	50–59	60–69	70+	Age—Adjusted to Mass 1940
1927	14 6	26 1	8 2	0	14 5
1928	27 3	19 4	24 3	0	24 0
1929	11 2	15 2	25 1	0	12 4
1930	15 4	21 3	10 7	12 9	15 6
1931	22 2	25 4	10 2	0	19 8
1932	33 0	20 8	29 9	9 4	29 3
1933	33 2	28 8	13 9	0	28 2
1934	26 5	12 1	29 5	22 1	24 5
1935	26 3	32 4	26 2	0	25 3
1936	29 4	21 4	23 3	29 2	27 6
1937	36 3	20 5	28 1	27 3	32 6
1938	28 7	27 6	25 6	18 7	27 5
1939	32 1	22 1	20 8	15 5	28 1
1940	38 5	18 0	28 2	22 3	33 1
1941	32 4	17 0	10 6	10 5	26 5
1942	21 6	26 6	19 2	22 1	21 2
Trend coefficient	1 06	0 03	0 35	1 51	0 87
σ Trend	0 31	0 31	0 13	0 16	0 26
Trend/σ trend	3 1	0 1	0 8	3 3	3 3

After Lombard, Bennett, Drake and Quinn (30) 1952

TABLE 89

Five Year Survival Rates After Radical Mastectomy During Different Five Year Periods

Period of Operation	With Metastasis			Without Metastasis			Totals		
	No. traced	No.	%	No. traced	No.	%	No. traced	No.	%
1910–1914	303	71	23.4	214	134	62.6	517	205	39.7
1915–1919	592	155	26.2	294	210	71.4	886	365	41.2
1920–1924	650	154	23.7	360	252	70.0	1 010	406	40.0
1925–1929	762	248	32.5	399	308	77.2	1 161	556	47.9
1930–1934	612	216	35.3	403	329	81.6	1 015	545	53.7
1935–1939	662	268	40.5	589	482	81.8	1 251	750	60.0
1940–1944	741	292	39.4	735	629	85.6	1 476	921	62.4
Total	4 331	1 406	32.5	2 994	2 344	78.3	7 325	3 750	51.2

* Calculations based upon patients traced (after Harrington (17))

between 1936 to 1938 and 1946 to 1948 for all white women with cancer The specific decline in death rate for insured women with breast cancer was recorded as 4 per cent during this same period

The five year survival rates following radical mastectomy have been reported by Harrington (17) during successive five year periods between 1910 and 1944 (table 89) A very definite and consistent increase in the survival rate was noted in both the group with axillary metastases and in the group without axillary metastases There is no apparent reason to suspect that patients during more recent years survived longer because they represent a lower grade of malignancy or bear tumors with a more benign biologic behavior It would seem that the improvement in postoperative longevity must be due to earlier diagnosis and more effective treatment

Wilfred Trotter is quoted by Smithers as having said that "one universal law has always governed the evolution of knowledge it is that progress is directly proportional to the closeness of the relation of the inquirer and the facts These then are the statistical facts Whatever we think them or wish them to be they represent the results of our accumulated experience that chill touchstone whose sad proof reduces all things from their hue"

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CHAPTER XX

Cancer of the Breast in the Male

Breast tumors in general, and cancer of the male breast in particular, have long stirred the imagination and interest of the surgeon, internist, pathologist, endocrinologist and general practitioner According to Gilbert (10), perhaps the earliest recorded reference to cancer of the breast in the male can be found in the writings of Franciscus Arcaeus (1493–1573) who noted that breast cancer was distinctly less common in the male as compared to the female Ambrose Paré (1510–1590), a celebrated French surgeon of the sixteenth century, is said to have been among the first to recognize this malignancy in the male Fabricius Hildanus (1537–1619) reported his observations of an original case of this disease and Louis Heister (1683–1758) discussed the details and description of the disease in his inaugural dissertation

The term "gynecomastia," an enlargement of the male breast resembling the female breast, was first used by Galen (130–200 A D) The condition was said to have been known to Aristotle, and Karsner (16), in a comprehensive study of gynecomastia, notes that it was also described in ancient and medieval times by Paulus Aegineta, Fabricius ab Aquapendente, Paracelsus, and other eminent men of medicine down through the ages

Systematic studies of cancer of the breast in the male have been the subject of at least two nineteenth century doctorate theses by Horteloup (1872) and Poirier (1883) Several years later, Schuchardt (1885) made a notable contribution to the clinical investigation of this disease (28) He reviewed the available literature and made elaborate statistical studies while tabulating more than 400 tumors of the male breast The vast majority of these tumors (86 per cent) were malignant Williams (35) reviewed 100 cases collected from various sources and published his results in a monograph on diseases of the breast (1894) This appears to be the earliest account of the disease in the British literature In America, S W Gross (1880) stated that the male is subject to the same neoplastic diseases of the breast as the female In a chapter discussing "tumors of the male mammary gland," Gross indicated that he had personal records of 102 patients with breast cancer, yet he had seen only two cancers of the male breast A collective review by Warfield (34), at the turn of the century, which appeared in the Bulletin of the Johns Hopkins Hospital, reported five new cases with a careful autopsy study

In more recent years, many noteworthy contributions to this subject have appeared in the medical literature Excellent reports and reviews have been published by Finsterer (8), Wainwright (33), Andrews and Kempneier (2), Neal and Simpson (23), Gilbert (10), Neal (22), Sachs (26), Peck (25), Karsner (16), Payson and Rosh (21), Jaaskeläinen (15), and Somerville (30)

Incidence

It is obvious to all that the incidence of breast cancer in the male is considerably less frequent than in the female. This is probably due, in part, to the vestigial structure of the male breast, as well as to the absence of hormonally induced cyclic changes. Sarcoma, however, is relatively more common among breast malignancies in the male as compared to the female. This probably reflects the quantitative predominance of connective tissue in the male breast. Figures have been reported by different investigators indicating the incidence of breast cancer in the male as compared to the female (table 90).

In an excellent clinicopathologic survey of 221 different tumors of the male breast, Jääskeläinen found 185 cases of gynecomastia (84 per cent), 22 cases of carcinoma (10 per cent), two cases of sarcoma (one per cent), nine cases of benign tumors (four per cent) and three cases of inflammatory conditions (one per cent). Neal reviewed 165 tumors of the male breast and found 30.3 per cent to be carcinoma, 6.1 per cent to be sarcoma, and 63.6 per cent to be benign breast diseases. Thus, although it is apparent that the relative incidence of malignant and nonmalignant tumors of the male breast will vary widely in accord with the material and criteria of each survey, in the differential diagnosis of these lesions it must be remembered that benign breast tumors, and in particular gynecomastia, are considerably more common than breast cancer.

Etiology

Age

The average age of onset of breast cancer appears to be slightly higher in the male than in the female. The youngest male patient with breast cancer that has been reported is a boy of 12, noted by Blodgett (4) and the oldest male patient with breast cancer is a man of 93 reported by Characho (5). Table 91 records the age incidence of breast cancer in the male as reported by several investigators.

Male patients with benign breast lesions and male patients with breast sarcoma both have a much lower average age incidence than patients with breast cancer.

Heredity

It is difficult to establish any pattern of hereditary predisposition in cancer of the male breast because of the relative infrequency of the disease and the unreliability of family history data. However, heredity is usually regarded as of secondary importance in the etiology of breast cancer in the male. A positive family history of cancer was noted in four out of 17 patients reported by Judd, in two out of 11 patients reported by Finsterer, in three out of 25 patients reported by Payson and Rosh, and in two

TABLE 90

Name	Total Breast Cancer	Male Breast Cancer	Per cent
Williams	1 870	16	0 9
Finsterer	602	11	1 0
Geschickter	2 551	30	1 2
Lewis and Rienhoff	950	0	0 0
Jääskeläinen	1 100	13	1 1
Payson and Rosh	1 141	25	2 2

TABLE 91

Name	Number of Cases	Age		
		Youngest	Average	Oldest
Wainwright	325	23	54 2	—
Neal	60	30	57 7	89
Sachs	194	12	57 2	86
Payson and Rosh	25	29	58 6	82
Jääskeläinen	22	39	56 8	76

CHAPTER XX

Cancer of the Breast in the Male

Breast tumors in general, and cancer of the male breast in particular, have long stirred the imagination and interest of the surgeon, internist, pathologist, endocrinologist and general practitioner According to Gilbert (10), perhaps the earliest recorded reference to cancer of the breast in the male can be found in the writings of Franciscus Arcaeus (1493–1573) who noted that breast cancer was distinctly less common in the male as compared to the female Ambrose Paré (1510–1590), a celebrated French surgeon of the sixteenth century, is said to have been among the first to recognize this malignancy in the male Fabricius Hildanus (1537–1619) reported his observations of an original case of this disease and Louis Heister (1683–1758) discussed the details and description of the disease in his inaugural dissertation

The term "gynecomastia," an enlargement of the male breast resembling the female breast, was first used by Galen (130–200 A D) The condition was said to have been known to Aristotle, and Karsner (16), in a comprehensive study of gynecomastia, notes that it was also described in ancient and medieval times by Paulus Aegineta, Fabricius ab Aquapendente, Paracelsus, and other eminent men of medicine down through the ages

Systematic studies of cancer of the breast in the male have been the subject of at least two nineteenth century doctorate theses by Horteloup (1872) and Poirier (1883) Several years later, Schuchardt (1885) made a notable contribution to the clinical investigation of this disease (28). He reviewed the available literature and made elaborate statistical studies while tabulating more than 400 tumors of the male breast The vast majority of these tumors (86 per cent) were malignant Williams (35) reviewed 100 cases collected from various sources and published his results in a monograph on diseases of the breast (1894) This appears to be the earliest account of the disease in the British literature In America, S. W Gross (1880) stated that the male is subject to the same neoplastic diseases of the breast as the female In a chapter discussing "tumors of the male mammary gland," Gross indicated that he had personal records of 102 patients with breast cancer, yet he had seen only two cancers of the male breast A collective review by Warfield (34), at the turn of the century, which appeared in the Bulletin of the Johns Hopkins Hospital, reported five new cases with a careful autopsy study

In more recent years, many noteworthy contributions to this subject have appeared in the medical literature Excellent reports and reviews have been published by Finsterer (8), Wainwright (33), Andrews and Kempneier (2), Neal and Simpson (23), Gilbert (10), Neal (22), Sachs (26), Peck (25), Karsner (16), Payson and Rosh (24), Jaaskelàinen (15), and Somerville (30)

Incidence

It is obvious to all that the incidence of breast cancer in the male is considerably less frequent than in the female This is probably due, in part to the vestigial structure of the male breast as well as to the absence of hormonally induced cyclic changes. Sarcoma however, is relatively more common among breast malignancies in the male as compared to the female This probably reflects the quantitative predominance of connective tissue in the male breast Figures have been reported by different investigators indicating the incidence of breast cancer in the male as compared to the female (table 90)

In an excellent clinicopathologic survey of 221 different tumors of the male breast Jääskeläinen found 185 cases of gynecomastia (84 per cent) 22 cases of carcinoma (10 per cent), two cases of sarcoma (one per cent) nine cases of benign tumors (four per cent) and three cases of inflammatory conditions (one per cent) Neal reviewed 165 tumors of the male breast and found 30.3 per cent to be carcinoma 6 1 per cent to be sarcoma and 63 6 per cent to be benign breast diseases Thus, although it is apparent that the relative incidence of malignant and nonmalignant tumors of the male breast will vary widely in accord with the material and criteria of each survey in the differential diagnosis of these lesions it must be remembered that benign breast tumors, and in particular gynecomastia, are considerably more common than breast cancer

Etiology

Age

The average age of onset of breast cancer appears to be slightly higher in the male than in the female The youngest male patient with breast cancer that has been reported is a boy of 12 noted by Blodgett (4) and the oldest male patient with breast cancer is a man of 93 reported by Charache (5) Table 91 records the age incidence of breast cancer in the male as reported by several investigators

Male patients with benign breast lesions and male patients with breast sarcoma both have a much lower average age incidence than patients with breast cancer

Heredity

It is difficult to establish any pattern of hereditary predisposition in cancer of the male breast because of the relative infrequency of the disease and the unreliability of family history data However heredity is usually regarded as of secondary importance in the etiology of breast cancer in the male A positive family history of cancer was noted in four out of 17 patients reported by Judd in two out of 11 patients reported by Finsterer in three out of 25 patients reported by Payson and Rosh and in two

Table 90

Name	Total Breast Cancer	Male Breast Cancer	Per cent
Williams	1 870	16	0 9
Finsterer	602	11	1 6
Geschickter	2 551	30	1 2
Lewis and Rienhoff	950	9	0 9
Jääskeläinen	1 190	13	1 1
Payson and Rosh	1 141	25	2 2

Table 91

Name	Number of Cases	Age		
		Youngest	Average	Oldest
Wainwright	325	23	54 2	—
Neal	50	30	57 7	89
Sachs	194	12	57 2	86
Payson and Rosh	25	20	56 6	82
Jääskeläinen	22	39	56 8	76

out of 18 patients reported by Jaaskelainen Yet, the latter author reported an even higher incidence of positive family histories for cancer in a similar series of gynecomastia patients Jaaskelainen concluded that "heredity probably is of little significance in the development of malignant tumours of the male breast" The tendency for gynecomastia to develop into breast cancer remains equivocal and it is extremely doubtful whether this lesion should be considered as precancerous

Race

Cancer of the breast in the male has been reported as having been clinically observed in all races and from almost every geographical part of the world There are case reports from India, China, Africa, and from most European countries and the Americas as well There is no valid statistical evidence to indicate a racial predominance for either whites or Negroes

Trauma

Bearing in mind how exposed the anterior chest wall is in the male to the incidental injuries of everyday life, it may be presumed that trauma has little or no relationship to the etiology of breast cancer (see Chapter VIII) However, this point of view is not accorded universal acceptance Gilbert reported that a previous history of injury was noted in 29 per cent of the patients in his series of male breast cancer A single severe injury was reported in 12 out of 14 patients, whereas two patients exerted pressure against their chest wall while following their usual occupation As noted by Gilbert, the previous integrity of the patient's breast and the authenticity of the trauma rest entirely upon the unverified statements of the patients themselves The position of the tumor in relation to the site of injury was not determined.

It is, of course, of the utmost importance to obtain a critical history of the exact sequence of events Yet, despite the difficulty of establishing a positive relationship between injury and breast cancer in the male, one cannot help but be impressed by the striking coincidence of an exceptional case showing a singular relationship between trauma and tumor Wainwright mentions a case of breast cancer resulting from a sword thrust, Billroth a tumor developing six months after a gunshot wound, Bryan records the history of a boy of 12 who developed breast cancer after a golf ball injury, Peck noted a case of breast cancer after an automobile accident in which three ribs were fractured, and Payson and Rosh reported a case of breast cancer following an injury from a chair Somerville suggests that such occupations as shoemaking, carpentry and mail-carrying may be particularly prone to incrimination as etiologic agents because of the factor of *chronic* irritation

Jaaskeläinen, on the contrary, found that trauma was a factor in only one case out of 20 in his survey of breast cancer, whereas in a similar survey of gynecomastia, trauma appeared to be an etiologic agent in ten cases out of 88 The time relationship between trauma and tumor development was usually long In a study of 19 cases of breast cancer in the male, Somerville could find only one patient who indicated an injury This incident occurred only a few days before hospital admission and probably served merely to call the patient's attention to his breast tumor

In the relationship between trauma and breast cancer, I am in accord with Ewing who expressed the opinion that "traumas reveal more malignant tumors than they cause"

Endocrine Influence

There is convincing clinical and experimental evidence of a close relationship be-

tween the sex hormones and breast cancer (see Chapter III) As early as 1825 Aitken suggested a possible connection between tumors of the breast and pelvic disease In 1829 Astley Cooper (6) discussed the functional relationship between the ovary and the breast but it was not until 1896 that oophorectomy was first advised and practiced by Beatson (3) as a means of treating breast cancer

Much of our present day knowledge of breast cancer is based upon animal experimentation (see Chapter IV) The carcinogenic potency of the ovaries was first demonstrated by Lathrop and Loeb (20) and their co-workers They found that the removal of both ovaries considerably reduced though did not entirely prevent the incidence of mammary cancer in mice Also in mice and rats, cancer of the breast can be produced by the intensive and prolonged administration of estrogens The pioneer studies of Goormaghtigh and Amerlinck (11) demonstrated the cystic changes which occur in the castrate female mouse breast after prolonged estrogen stimulation The classic work of Lacassagne (19) indicated that characteristic mammary cancer in male mice could be produced in response to estrogenic stimulation These mice belonged to a high cancer strain but malignant mammary tumors ordinarily did not spontaneously occur in the male

Scarff and Smith (27) have reported the biopsy findings of marked epithelial proliferation occurring in two men employed in the manufacture of stilbestrol However Foote and Stewart (9) in a comparative study of cancerous versus non-cancerous breasts concluded that epithelial hyperplasia induced by estrogens differs from that seen in neoplasia

Yet in 1948 Abramson and Warshawsky (1) reported the case of a 51 year old Negro who was treated with stilbestrol over a long period of time for metastatic cancer of the prostate At autopsy sections taken from one breast revealed carcinoma The following year Howard and Grosjean (13) reported the case of a man with cancer of the prostate who received 40,280 mgm. of diethylstilbestrol (stilbestrol) over a five year period At the time of death bilateral scirrhous carcinoma of the breast was present Graves and Harris (12) have reported a more convincing case of primary breast cancer with axillary metastasis following estrogen therapy for prostate cancer in which there were no other demonstrable metastases from the prostate elsewhere in the body There is every likelihood that this represents a case of primary breast cancer rather than metastatic prostate cancer Acid phosphatase studies of the tissue would have aided in this differential diagnosis The patient was treated by radical mastectomy with early apparent success

The rarity of cancer of the breast in the male may be partly attributable to the usual lack of hormonal stimulation which in the female causes cyclic physiologic breast engorgement and hypertrophy associated with menstrual activity enlargement during pregnancy and lactation changes Recent work in endocrinology has indicated that the ovaries are largely but not entirely responsible for the induction of breast cancer Although the ovaries secrete most of the estrogenic hormone under certain conditions they are also capable of secreting androgens It is known that the Sertoli cells of the testes can secrete estrogens and the adrenal cortex can elaborate both estrogens and androgens It has been suggested for instance that cancer of the male breast can be attributed to the secretion of estrogens by the testes

On the basis of most clinical investigative results it can be concluded that the genital diseases noted during physical examination have no significant bearing on the etiology of breast cancer in the male Although the medical literature has certain sporadic case

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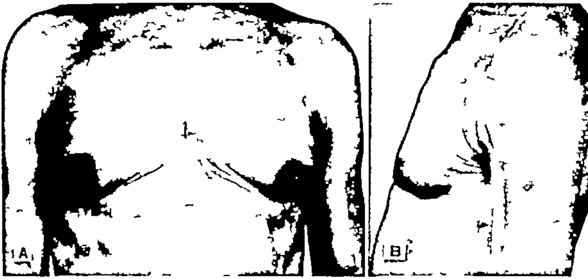

FIG 178 A FIG 178 B

FIG 178 A and B Bilateral gynecomastia (hormonal type) front view and profile

well. The fact that this patient had bilateral involvement at different times, is very unusual and one would think that perhaps there was an underlying hormonal etiology However such an etiology cannot be discovered in the majority of cases

HORMONAL TYPE OF GYNECOMASTIA

Gynecomastia can result from an excess of either estrogen or androgen The former as an etiological agent is well known and easily understood since it has been known for a long time that estrogen is the most important stimulus for breast growth Since 1936 it has been known that androgen can cause development of mammary tissue in both male and female animals (Selye McEuen and Collip (29)) and gynecomastia has been observed in eunuchoid males treated with androgens (Kriss (18)) (McCullagh (21)) The hormonal types of gynecomastia therefore, will be discussed separately and subdivided into those types produced by estrogens, androgens and other steroid hormones.

Estrogen

Estrogens are used therapeutically in males and often cause gynecomastia. The gynecomastia produced by prolonged estrogen administration persists even after the stimulus is removed and normal hormonal balance attained There is no known hormone therapy that will resolve this dense connective tissue proliferation and surgical excision is the treatment of choice

Estrogen may be secreted by testicular tumors (chorionepitheliomata and Sertoli cell tumors) and by adrenal cortical tumors with resulting gynecomastia

The gynecomastia of the newborn is due to the excess estrogen circulating in the maternal blood during pregnancy (fig 179 A and B) These infant breasts sometimes secrete a small amount of cloudy fluid the so-called witches milk' of the newborn

Gynecomastia occurs fairly frequently in cirrhosis of the liver and in a variety of other conditions associated with disturbances in nutrition and liver function (hyperthyroidism starvation ulcerative colitis pulmonary disease and tuberculous meningitis)

The cause of the gynecomastia in these patients is a relative excess of circulating estrogens because of failure of the liver to inactivate these substances It is generally accepted that liver disease may interfere with inactivation of estrogens experiments

FIG 177 Bilateral gynecomastia in an adult man

ports of breast cancer developing in gynemastia, it is highly unlikely that this type diffuse fibro-epithelial hypertrophy will use cancer of the male breast

Gynecomastia

As noted previously, gynecomastia litery means "female breast" and is used to note an increased size of the male mamry gland It is important to differentiate e gynecomastia from psuedogynecostia, which is simply adipose tissue A nbination of the two may, of course, cur

Clinically, gynecomastia may occur in any gree, from a small disk of tissue under one ple (which is the usual finding in adolest hypertrophy) to marked enlargement both breasts (fig 177) It is often unieral, but the hormonal type is usually ateral, although one breast may be larger n the other Occasionally, secretion of a ar fluid may be found, true lactation is remely rare, but one patient with a ateral "milky" secretion has been obved The breast may be tender or sensie, but patients usually present themves because of the undesirable cosmetic ect The areolae may or may not be mented

Pathologically, gynecomastia presents a typical picture There is much fibrous connective tissue stroma, which may be dense or loose, in which there are many or few ducts but no acini Around the ducts there is often a clear zone in which the stroma is less dense It is impossible to tell microscopically what has caused the gynecomastia and whether or not it is of endocrine origin Many such sections have been studied and no definite correlation has been found between either the hormonal or the non-hormonal types

NON-HORMONAL TYPE OF GYNECOMASTIA

In most cases gynecomastia is unilateral and of unknown etiology A case in point is that of a 25 year old man who noticed a lump in the left breast in the summer of 1949 There were no other symptoms or findings, and the lump spontaneously disappeared It recurred in the spring of 1950 and was excised in November, 1950 The right breast at that time was normal In the summer of 1951, the right breast began to enlarge and a small amount of clear fluid could be expressed The tissue of the right breast was excised in September, 1951 There were no other abnormalities present on physical examination and the patient has remained

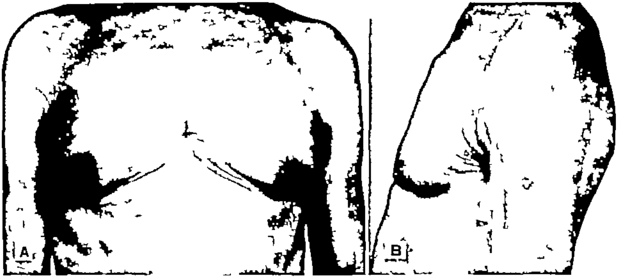

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Fig 179 A

Fig 179 B

Figs 179 A and B Gynecomastia of the newborn showing regression during the first few weeks of infancy The so-called "witches' milk" is often secreted during this time

in rats have shown that vitamin B complex deficiency interferes with inactivation of estrogens, but not androgens, by the liver Thus, in malnutrition or during recovery from malnutrition if there is impairment of liver function, a relative increase in circulating estrogens with resulting gynecomastia may occur

Androgen

Androgens, testosterone and its derivatives, are frequently used in treating males and may cause gynecomastia A 42 year old man had been taking very large doses of methyl testosterone and later testosterone propionate for six years for psychogenic impotence. This resulted in marked bilateral gynecomastia and azoospermia The breast tissue was excised and a testicular biopsy obtained. Spermatogenesis was markedly impaired He was persuaded to stop testosterone and was treated with psychotherapy One year later his sperm count was normal and his wife four months pregnant This long continued use of testosterone had not permanently damaged his testes

Androgen treatment of a eunuchoid or castrate patient may cause gynecomastia which usually subsides gradually but may require surgical excision Increased androgen production following administration of anterior pituitary like hormone has caused gynecomastia which regresses when therapy is stopped Interstitial cell tumors of the testis and tumors of the adrenal cortex may produce large amounts of androgen and cause gynecomastia

At puberty gynecomastia usually mild occurs in the majority of boys. This is probably due to a relative transient increase in androgen During puberty the interstitial cells are the first to become active and there is an increase in androgen before the seminiferous tubules fully develop Gynecomastia occurs and then gradually subsides as the tubular epithelium develops and Sertoli cells appear In rare cases however, it persists and requires surgical excision

Relative excess of androgen also occurs in various conditions where the seminiferous tubular epithelium either fails to develop or is destroyed by X rays, infection or trauma. In this situation, the testes are small, there is azoospermia and fairly normal Leydig or interstitial cell function The excretion of FSH in the urine is high indicating that some pituitary inhibiting hormone is not being secreted by the testis Gynecomastia commonly occurs and can best be treated by excision

Other Steroid Hormones

Desoxycorticosterone and cortisone have caused gynecomastia in patients treated for Addison's disease and collagen disease respectively The mechanism is unknown and it occurs only very rarely It is possible that these hormones are converted into estrogens or that they stimulate the breast directly

In paraplegics and in some patients with degenerative lesions of the spinal cord gynecomastia not uncommonly occurs and the etiology is unknown One would suspect that it results from a relative increase in either androgen or estrogen but hormone assays have not shown that a definite imbalance exists

Differential Diagnosis

Duration

The duration of the disease in the male is usually longer than in the female. In view of the sparsity of breast tissue in the male one might have expected breast cancer to have been discovered earlier and the duration of the disease to have been shorter However other factors such as a slow rate of growth and a lack of breast consciousness in the male may account for this paradoxical situa

TABLE 92

Name	Total Cases	Duration of Disease Less than One Year	
		No	Per cent
Williams	96	22	23
Wainwright	342	161	47
Gilbert	47	26	55
Neal	27	18	67
Sachs	174	106	61
Geschickter	30	18	60
Jääskelainen	20	10	50

tion of delayed recognition Figures are given by different investigators (table 92) for the percentage of patients seeking treatment within one year after onset of the disease (after Jaaskelainen).

Breast Tumor

The primary complaint of almost all patients with breast disease, whether benign or malignant, is usually the discovery of a "lump" in the breast In cancer of the breast in the male the size of the tumor may vary considerably, depending upon its rate of growth, the duration of disease and the discomfort caused the patient Breast cancer is most often of a very firm consistency although, surprising as it may seem, gynecomastia and certain benign tumors may also appear to be quite hard and fixed to the subareolar tissue Jaaskelainen found 70 per cent of the malignant tumors fixed to the overlying nipple and skin and 65 per cent of the breast enlargements due to gynecomastia similarly attached Cancer of the male breast is almost always unilateral except as noted previously during estrogen therapy, whereas gynecomastia may be bilateral in about ten to 20 per cent of the patients

Pain

Gilbert noted that pain was present in only 27 per cent of the patients Payson and Rosh indicated that pain was a late symptom, usually occurring with ulceration or nipple retraction Tenderness to palpation was present in about 60 per cent of Jaaskelainen's breast cancer series but was an even more prominent symptom of gynecomastia

Retraction Signs

Nipple retraction and skin fixation in the male breast may occur in conjunction with either benign or malignant breast diseases This is due to the small volume of breast tissue and the close proximity of the pathologic process to the terminal ducts Nipple retraction occurred in 33 per cent of Sachs' series, 29 per cent of Gilbert's series, and 32 per cent of the cancer cases reported by Payson and Rosh However, in this latter series, 68 per cent had attachment to the overlying skin Payson and Rosh noted that 44 4 per cent of the benign breast diseases in their series also had *fixation of the skin*, which adds to the difficulty of differential diagnosis

The various tests described in Chapter VIII are usually not necessary to accentuate the signs of retraction in the male breast

Ulceration

Even considering the small amount of breast parenchyma and adipose tissue in the male, the percentage of patients with the distressing sign of ulceration seems unusually high Wainwright found ulceration to be present in 38 per cent of his collected series, Payson and Rosh in 28 per cent and Sachs in 29 per cent of his group of cases

Nipple Secretion

Bleeding from the nipple is an uncommon sign which usually occurs late in the disease Paget's disease in the male, giving rise to nipple secretion, is *extremely rare* Wainwright states that "a discharge from the nipple is a more frequent and a more danger-

ous signal in men than in women ' In Gilbert's series, bleeding from the nipple occurred in only eight per cent of the patients

Axillary Involvement

The positive involvement of the axillary nodes in a high percentage of patients is presumably due to the paucity of breast tissue, the prolonged period between onset of the disease and treatment and the anatomical ease of lymphatic dissemination between the breast and the axilla in the male These factors facilitate both local invasion and regional metastatic spread

Axillary metastases verified by histologic examination were found to be present in 80 per cent of Peck's series Payson and Rosh reported that 72 per cent of their patients were clinically diagnosed as positive but only 60 per cent proved to have axillary metastases on pathologic examination Axillary involvement is mentioned by Wainwright in 68 per cent of his series by Sachs in 48 per cent and by Somerville in 61 per cent of his patients

Enlarged axillary nodes were present in 45 per cent of Jääskeläinen's series of breast cancer cases but a similar enlargement was noted in 23 per cent of the gynecomastia cases On physical examination the axillary nodes in breast cancer are frequently hard *and fixed in contrast to those occurring in* gynecomastia. Axillary involvement in the male may be the precipitating factor in bringing the patient to the doctor This is rarely the initial complaint in the female

Pathology

In an excellent article on this subject Neal (22) states that the pathologic variations between the malignant growths of the male and of the female breast are those of degree and ratio of types and not of kind The growths of the male breast are indistinguishable from similar tumors more commonly found in the female breast Thus despite variations in classification there appears to be little basic difference in the pathology of breast carcinoma between the male and female (see Chapter V)

Inflammatory carcinoma of the male breast is a rare but most interesting clinical

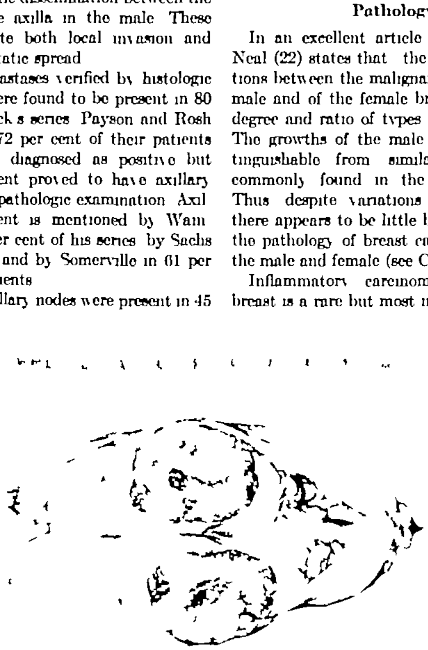

FIG 180 Gross specimen of cancer of the male breast showing relatively large tumor in comparison with surrounding breast tissue

variant It can occur with any pathologic type of carcinoma Treves (32) has reported three cases of this particularly virulent form of breast cancer in 131 males with mammary malignancy Two of these patients had primary inoperable lesions, one unilateral, the other bilateral The prognosis was extremely poor

Martineau and Goodrich have surveyed the literature of Paget's disease of the male breast and found it to be an exceedingly rare condition Seventeen cases in addition to theirs were collected from the literature All cases showed characteristic Paget's cells in the epidermis, most cases revealed an eczematoid nipple lesion and a duct-cell carcinoma was found beneath the nipple or areola on careful microscopic examination The prognosis was poor despite a variety of surgical therapeutic procedures

Metastases

As the disease becomes clinically more advanced, regional and remote metastases develop An analysis of the large series reported by both Wainwright and Sachs indicates the distribution of distant metastases to be quite similar to the metastatic spread in the female The predominant sites are the regional lymph nodes, lungs and skeletal system

Treatment

The principles of treatment for cancer of the male breast are exactly the same as those described previously for cancer of the female breast Radical mastectomy, when clinically indicated, sets a high standard of surgical treatment and remains the operation of choice for most cases of breast cancer in the male Because of the sparsity of breast tissue, skin closure almost always requires grafting Postoperative radiotherapy is recommended for all patients with axillary metastases by microscopic examination

The same criteria of inoperability (see Chapter XI) are applicable regardless of sex Male patients considered categorically "inoperable" for radical mastectomy may be suitable candidates for simple mastectomy and postoperative radiotherapy Palliative radiotherapy alone may be indicated as a useful adjunct to castration and hormone therapy in patients with advanced disease

In 1942, Farrow and Adair (7) first reported the beneficial effects of orchiectomy on skeletal metastases in cancer of the male breast. Since then Treves (31) has surveyed the literature and reported an additional 13 carefully studied cases of breast cancer in the male treated by surgical castration The influence of hormones is being widely investigated and the therapeutic effect of the sex steroids in breast cancer is the subject of intensive clinical inquiry (see Chapter XVI) Castration and endocrine ablation for breast cancer in both the male and female have been advocated as a means of decreasing neoplastic activity by the removal of critical amounts of hormones secreted by these endocrine organs The results of orchiectomy in cancer of the male breast are quite striking in some cases and are closely parallel to those observed in cancer of the prostate

Treves reports that bilateral orchiectomy has had definite favorable effects on male breast cancer and is recommended as an important therapeutic adjunct in advanced, inoperable or metastatic cancer Our experience supports these findings and we have observed the gratifying subjective response of complete pain relief in some patients with bone metastases, particularly to the spine. Whereas a single patient may occasionally present a unique, long-term, spectacular remission, favorable objective regression is for the most part transient and unpredictable

There is but little evidence to recommend *prophylactic* orchiectomy performed at the

time of radical mastectomy as a means of enhancing survival However bilateral surgical castration is advocated as a *therapeutic* measure for all patients with inoperable recurrent or metastatic disease

Huggins and Dao (14) have treated two male patients with advanced breast cancer by means of bilateral adrenalectomy Both patients had previously been subjected to orchiectomy One patient with pleural effusion responded well and the other patient succumbed without benefit The clinical experimental results of hypophysectomy in the male may be expected to be quite similar to those in the female

Kennedy and Nathanson (17) among others have used intensive estrogenic therapy in the hormonal treatment of advanced breast cancer in men (fig 181 A and B) The objective and subjective response appeared to be favorable and quite comparable to that noted in women (see Chapter XVI) The side-effects of therapy included anorexia, nausea vomiting pigmentation of the nipple and gynecomastia of the contralateral breast

Early diagnosis and immediate radical mastectomy are imperative for the male patient with breast cancer who is amenable to operative treatment However when the disease has advanced beyond the stage of operability it is prudent to resort to less specific surgery and such palliative benefits as radiotherapy castration and hormone therapy Although life expectancy may be merely provisionally prolonged and the freedom from pain afford but a temporary mercy yet to the patient in despair these comforts can be a most fortuitous blessing

Endocrine therapy is one of the most interesting and promising fields in breast cancer research However until much more is known of sex steroid metabolism there is little likelihood of improving the results of hormone therapy by heroic attempts at either endocrine elimination or somatic reduction.

End-Results

The end results in the treatment of cancer of the breast in the male are generally regarded as poor The reasons for this unfavorable prognosis are frequently given as (1) patient delay in seeking treatment, (2) doctor delay in making the diagnosis, (3) anatomy of the male breast favors the more rapid extension of the disease to the regional nodes.

In the series of Payson and Rosh (24), 10 out of 25 cases were considered "operable" when first examined Yet of these 10 patients only nine actually received the benefit of a complete radical mastectomy Jääskelämen reported that less than half (nine out of 22) of his cases underwent radical mastectomy Gilbert considered that only 30 per cent of a total series of 40 patients could be classified as "operable on admission However, in a more recent study, Somerville reported that 84 per cent of the patients were operable" and all of these were treated by radical mastectomy

The absolute five year survival rate for Somerville's series of 19 cases (three cases operated upon less than five years ago) was only 19 per cent Wainwright collected a total of 418 case reports and of these the end results were known in only 163 cases The five year survival rate of these known cases was also 19 per cent Jääskelämen reported a five year survival rate of 14 per cent In the series of Payson and Rosh, only 16 out of 25 cases were followed for five years. It is interesting to note that the five year survival rate of this group was 50 per cent (absolute survival rate of 32 per cent), but the five year "cure" rate was only 18.8 per cent (absolute "cure" rate of 12 per cent) Thus, it is apparent that many patients were alive with recurrences and

FIG 181 A

FIG 181 B

FIG 181 A Multiple pulmon[illegible] and osseous metastases in a 70 y[illegible] old man five years after radical m[illegible] tectomy

B Six months after orchiecto[illegible] and continuous estrogen therapy [illegible] tient has remained well for two a[illegible] one half years and has returned [illegible] part-time work

metastases at the end of five years who ultimately succumbed to their disease The prognosis of patients without axillary metastases, of course appears to be much better for both the male and female

Although the prognosis of cancer of the breast in the male is a distressingly somber story yet radical mastectomy and radiotherapy promptly performed provide the most effective means, at present of greatest possible benefit

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